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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

OCTOBER, 1951

ORIGINAL ARTICLES

PROCAINE AMIDE (PRONESTYL*) IN THE TREATMENT OF CARDIAC ARRHYTHMIAS†§

By J. Murray Kinsman, M.D.

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AND

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(From the Department of Medicine and the Institute for Medical Research, University of Louisville School of Medicine, Louisville)

Procaine was introduced by Einhorn in 1904. It was first given intravenously in 1909 by Bier, but for many years fear of its possible toxic effects when introduced so rapidly to the tissues of the body prevented its general use in this manner. Comparatively recently, however, there developed a widespread interest in the intravenous use of the drug, and experience rapidly began to demonstrate that so long as certain precautions were observed it was comparatively safe to use it in this way. It has now been employed for a great variety of conditions, especially during anesthesia for the prevention or correction of abnormal rhythms, particularly tachycardias.

On the heart, procaine has a digitalis-like action, reducing the irritability of the myocardium and the excitability of the cardiac intrinsic nerves, and prolonging the refractory period. It reduces blood pressure. It has a convulsive tendency through celebral action.

Until very recently, the hydrochloride was almost exclusively the form in which the drug was used. This derivative is rapidly hydrolyzed in the blood and is acetylated in the liver, so that its effects are comparatively fleeting. In 1949 the amide was introduced. Preliminary investigations in dogs by Mark and his co-workers[2] demonstrated that it prevented the development of epinephrine-induced ventricular arrhythmias under cyclopropane anesthesia; the same authors reported that its hypotensive and convulsive effects are less than those of the hydrochloride. The amide is hydrolyzed quite slowly and about 60% is excreted in the urine

* Supplied through the courtesy of E. R. Squibb and Sons.

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§ Presented in substance before the Association of American Physicians, Atlantic City, May 1, 1951.

unacetylated. Furthermore, it is absorbed well from the gastrointestinal tract as shown by effective blood levels following its oral administration.

Because of these factors, it was decided to investigate its effect on a variety of ectopic cardiac rhythms, and to obtain information regarding its safety. In order to obtain the most rapid action, only the intravenous route was used. Procaine amide (Pronestyl) is supplied by the manufacturer in ampules, each containing 1000 mg. in 10 cc. It was injected undiluted at a rate not over 200 mg. per minute, and usually at 100 mg. per minute. Practically continuous electrocardiograms were recorded during the injection period and at frequent intervals for some time following it. Blood pressures were taken very frequently throughout the entire period of the observations. Subjective and objective symptoms were noted and recorded.

TABLE 1.—SUMMARY OF ANTI-ARRHYTHMIC EFFECT OF PROCAINE AMIDE INJECTED INTRAVENOUSLY

Type of Rhythm	*Number of Arrhythmias Observed*	*Normal Rhythm Restored*
1. Normal rhythm (11 patients)		
2. Sinus tachycardia (acute infarction)	1	0
3. Paroxysmal auricular tachycardia	1	?
4. Auricular fibrillation	24	2
5. Auricular flutter	2	0
6. Auricular ectopic beats	4	3
7. Nodal tachycardia	1	0
8. Ventricular tachycardia	4	2
9. Ventricular ectopic beats	14	12
Total	51	(in 41 patients)

Effects on Arrhythmias. Procaine amide was given intravenously to 41 patients who exhibited a total of 51 arrhythmias (several patients having both auricular fibrillation and ectopic ventricular contractions) and to 11 patients with normal sinus rhythm. The details and the results are summarized in Table 1.

ARRHYTHMIAS OF AURICULAR ORIGIN. 1) *Sinus Tachycardia.* In 1 patient with simple sinus tachycardia following acute myocardial infarction, there was no appreciable effect on the heart rate.

2) *Paroxysmal Auricular Tachycardia.* In 1 patient with paroxysmal auricular tachycardia, the drug did not cause disappearance of the disturbance following a dose of 1000 mg. in 6 minutes. However, carotid sinus stimulation immediately following the injection was followed by abrupt restoration of normal sinus rhythm, whereas the same maneuver prior to the injection had been without effect. The role of procaine amide in this case is therefore somewhat speculative.

3) *Auricular Fibrillation.* In 22 patients with chronic auricular fibrillation, the drug had no effect in doses up to 1000 mg. In 2 patients with paroxysmal auricular fibrillation, however, normal sinus rhythm was restored following doses of 300 mg. and 550 mg. The transition occurred during the injection.

4) *Auricular Flutter.* In 2 patients with auricular flutter, no effect was obtained from 900 to 1000 mg., respectively. The flutter had been present for at least 6 days in 1 case, and 24 hours in the other.

5) *Auricular Ectopic Beats.* Of 4 patients with auricular ectopic contractions the ectopic beats were abolished in 3 following doses of 950 to 1000

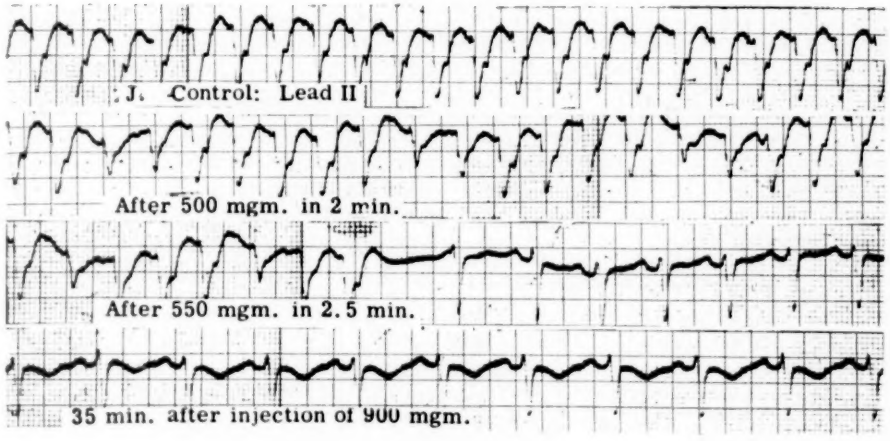

FIG. 1.—Ventricular tachycardia. Abrupt restoration of normal sinus rhythm after 550 mg. of procaine amide had been injected in 2.5 minutes.

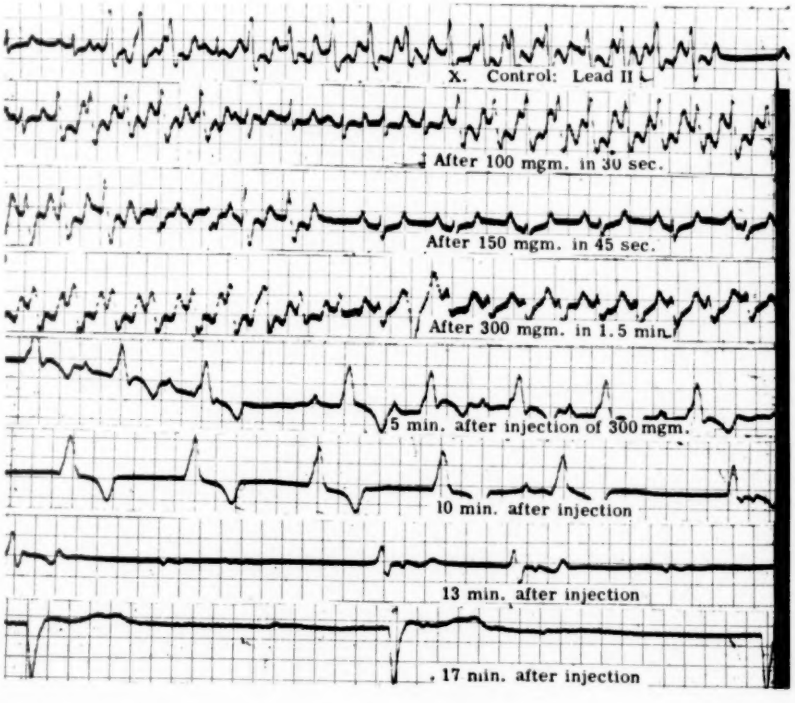
X. Control: Lead II
After 100 mgm. in 30 sec.
After 150 mgm. in 45 sec.
After 300 mgm. in 1.5 min.
5 min. after injection of 300 mgm.
10 min. after injection
13 min. after injection
17 min. after injection

FIG. 2.—Ventricular tachycardia. Patient was moribund when injection was started and died shortly after a small dose. Tachycardia was replaced by bradycardia, a-v block and nodal rhythm before death.

mg. In the fourth patient an auricular bigeminy was unaltered by 1000 mg.

ARRYTHMIAS OF A-V NODAL ORIGIN. *Nodal Tachycardia.* In 1 patient with tachycardia (rate 205) of nodal origin normal sinus rhythm did not follow the administration of 1000 mg., although 5 minutes later the rate had dropped to 165. The tachycardia had been present for at least 9 days.

ARRHYTHMIAS OF VENTRICULAR ORIGIN. 1) *Ventricular Tachycardia.* Procaine amide was administered to 4 patients with paroxysmal ventricular tachycardia. In 2, the tachycardia promptly stopped following doses of 450 and 550 mg., respectively (Fig. 1). One patient was moribund, the blood pressure being unobtainable when the injection was started. Death occurred 17 minutes after the injection, after only 300 mg. had been given (Fig. 2). This patient had had an acute infarction 4 hours previously and was the first patient with ventricular tachycardia treated with procaine, so extreme caution was exercised regarding dosage. The fourth patient also developed ventricular tachycardia 4 hours following myocardial infarction; when the injection was begun, the blood pressure was 116/74 and the patient was conscious and responsive. After 200 mg. had been administered in a period of 2 minutes, she suddenly gasped and died; the electrocardiogram showed ventricular fibrillation terminally (Fig. 3).

2) *Ventricular Ectopic Beats.* Of 14 patients with ventricular ectopic contractions, the ectopic beats were completely abolished in 12, following doses ranging from 200 to 1000 mg. The shortest duration of effect was 12 minutes (in 1 patient), while in another patient, there had been no known recurrence 7 days later. Almost invariably, however, they recurred after varying lengths of time, usually hours or days, but sometimes minutes. Where the pattern before treatment was one of bigeminy or trigeminy there was marked tendency toward resumption of the same pattern when the effects of the drug disappeared (Fig. 4). In one patient, the ectopic beats disappeared following administration of 250 mg. of procaine amide intravenously and had not reappeared when the patient left the laboratory, but in spite of

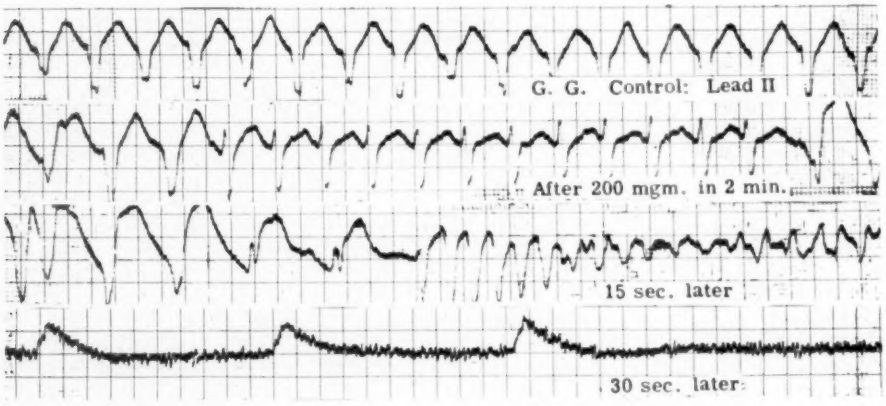

FIG. 3.—Ventricular tachycardia. Following a very small dose of procaine amide ventricular fibrillation developed and patient died within 3 minutes of beginning of injection.

L. S. Control: Lead II
After 450 mgm. in 3 min.
After 800 mgm. in 7.5 min.
After 900 mgm. in 9 min.
22 min. after injection of 900 mgm.
27 min. after injection
35 min. after injection
45 min. after injection

FIG. 4.—Illustrating temporary disappearance of ectopic ventricular contractions with trigeminy replaced by bigeminy, the latter by isolated ectopic beats which then disappear, and the reoccurrence of ectopic beats developing the same pattern in reverse order.

a "maintenance dose" of 3 gm. daily by mouth, they had reappeared 3 days later.

Of the 2 patients in whom the drug failed to abolish the ectopic contractions, one received 2000 mg. during a 1-hour period, and the other 1000 mg. in 8.5 minutes.

Toxic Effects. CLINICAL. *Subjective.* Seventy-five per cent of the patients had no significant subjective symptoms. In those who did, they were usually slight and in only 1 or 2 instances were they at all marked. The chief symptoms noted in these cases were flushing of the face or slight giddiness. Other symptoms occasionally encountered were bad taste in mouth, thirst, weakness, and nausea; one patient complained of substernal discomfort and of apprehension. None of the patients had convulsions, none died except the 2 with ventricular tachycardia following myocardial infarction, and in no instance were the subjective reactions sufficiently severe to cause alarm.

Objective. The heart rate was usually unchanged or slightly slowed; in a few instances it was slightly increased. The blood pressure practically always fell, the only exception being in the patient with nodal tachycardia (his blood pressure was 85/60 and remained at that level during the period of observation). The average fall for the surviving 50 patients was 32 for the systolic pressure and 13 for the diastolic, the greatest individual fall being 54 systolic and 32 diastolic (from 118/72 to

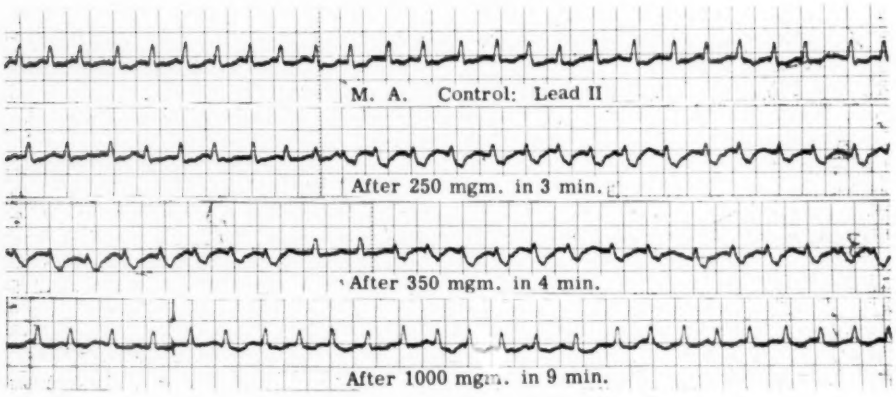

FIG. 5.—Illustrating absence of effect of procaine amide on auricular fibrillation and development of bundle branch block which was erratic and inconstant and disappeared even though the injection was continued.

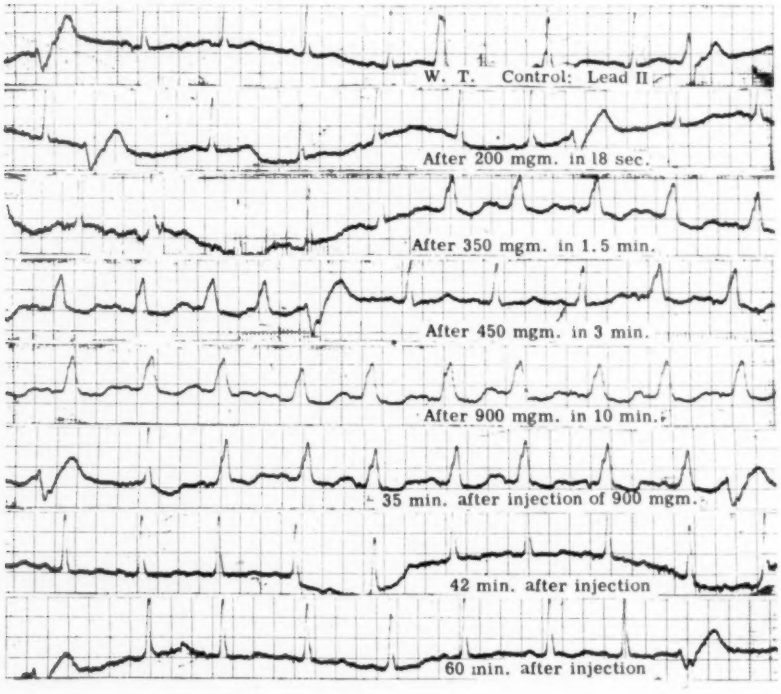
W. T. Control: Lead II
After 200 mgm. in 18 sec.
After 350 mgm. in 1.5 min.
After 450 mgm. in 3 min.
After 900 mgm. in 10 min.
35 min. after injection of 900 mgm.
42 min. after injection
60 min. after injection

FIG. 6.—Illustrating the sudden appearance of bundle branch block after 450 mg. of procaine amide had been injected in 3 minutes.

64/40) in one of the patients with auricular flutter. The degree of blood pressure fall was apparently less related to the total dosage than to the rate of injection, being more pronounced at faster rates. The duration of the hypotensive effect was seldom longer than 15 to 20 minutes following the discontinuance of the injection.

ELECTROCARDIOGRAPHIC. The one effect which was observed in practically every case (93%) was prolongation of the QRS complexes (Figs. 5 and 6). The records of 41 of the 50 surviving patients were carefully analyzed from this point of view, and these measurements are shown in Table 2, the maximum QRS duration *at any time* being reported. Study of this table reveals that in only 3 instances did the QRS complexes not lengthen; these 3 were all normal individuals without any evidence of heart disease, and each received a dose of 1000 mg. within 15 minutes. In 16 other cases, the maximum QRS duration recorded was still under 0.11 second. In 16 instances the initial measurement was under 0.11 second, but prolongation beyond 0.10 second resulted from the drug. In 6 instances defective intraventricular conduction was already present when the procaine was administered, and in each case there was an appreciable increase in the QRS duration. The degree of increment in the QRS duration ranged from zero (in the 3 normal individuals) to 0.11 second (increasing from .07 to .18 second in a patient with arteriosclerotic heart disease and ventricular ectopic contractions; the bundle branch block developed suddenly after 350 mg. had been injected in 90 seconds. The patient complained of dizziness and weakness, and the pulse remained unchanged, but the blood pressure dropped from 110/64 to 70/0. The blood pressure rose to 75/40 within 5 minutes, but the bundle branch block persisted for 30 minutes). In 27 of the 41 cases, the increment was from .02 to .04 second. The effects usually persisted from 20 to 50 minutes.

TABLE 2.—PROLONGATION OF QRS FROM PROCAINE AMIDE INJECTED INTRAVENOUSLY

Initial QRS Duration (second)	*Number of Cases Treated and Maximum QRS Duration Following Procaine (second)*												
	.06	*.07*	*.08*	*.09*	*.10*	*.11*	*.12*	*.13*	*.14*	*.15*	*.16*	*.17*	*.18*
.05			1	1									
.06	1		5		1		1						
.07			3								1		1
.08			2	1	4	2	3				1		
.09								2	1				
.10								3			1		
.11											4	1	
.12													
.13													
.14													
.15													
.16													1

Other untoward effects recorded electrocardiographically which were less pronounced and less frequent were transient flattening, notching, or inversion (rare) of the T waves, marked sinus arrhythmia, wandering of the pacemaker (Figs. 7 and 8) (2 instances), nodal rhythm (Fig. 8) (1 instance), ventricular escape (1 instance), and first degree a-v block (Fig. 8) (1 instance). Lesser degrees of increase in a-v conduction time were insignificant.

HEMODYNAMIC EFFECTS. In 10 patients, hemodynamic studies were car-

ried out by cardiac catheterization and the dye-injection method (modified) of Hamilton, Moore, Kinsman, and Spurling[4]. These studies are reported in detail elsewhere[3], but the conclusions may be summarized here.

The *radial artery pressure* fell in nearly every case, as had been observed clinically. It had usually, but not always, returned to the control level 30 minutes later.

The *pulmonary artery pressure* fell significantly in every case but one, in which it rose (one of those without heart disease). It had usually returned to the control level or above 30 minutes later, although in 4 instances it was still below the control level at that time.

The *mean circulation time* was usually significantly increased over the control level, returning to it in 30 minutes in most instances.

The *cardiac output* fell significantly

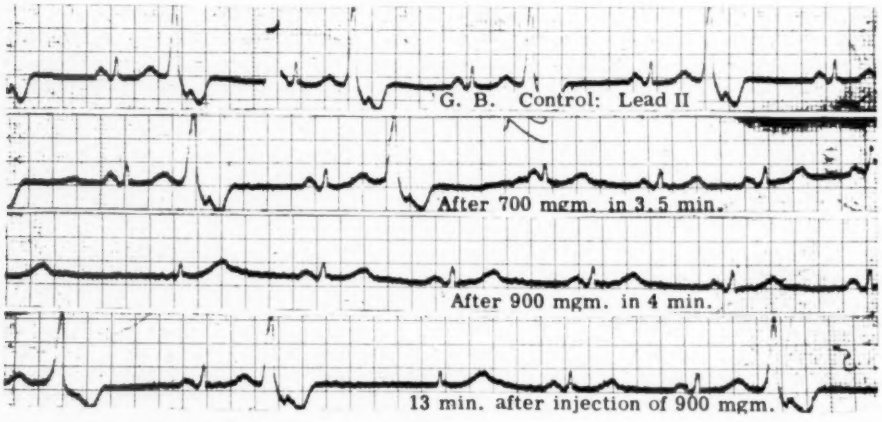

FIG. 7.—Illustrating temporary disappearance of ventricular ectopic contractions and development of sinus bradycardia and arrhythmia and wandering pacemaker.

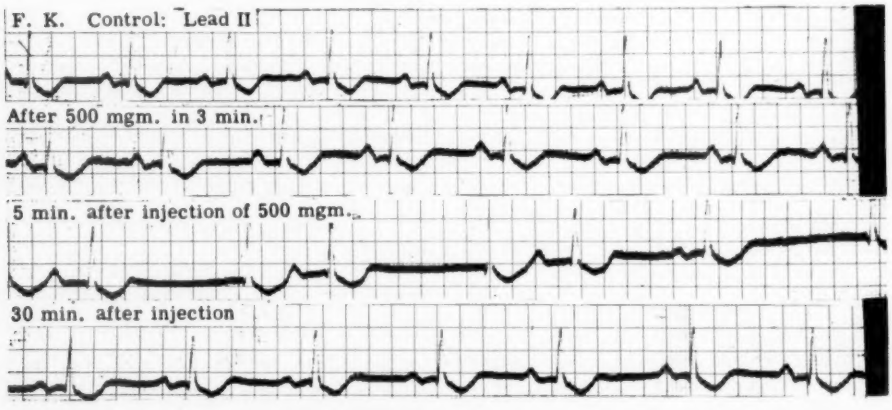

FIG. 8.—Illustrating the development of wandering pacemaker and nodal ectopic contraction and increase in an already slightly prolonged a-v conduction time.

from the control level in 5 of the patients, was not significantly altered in 4, and increased significantly in 1 (the patient whose pulmonary artery pressure rose). With 2 exceptions, the output had not returned to the control level 30 minutes later.

Discussion. That procaine amide, when administered by the intravenous route, has a very definite antiarrhythmic effect is quite obvious from these observations. The evidence for such an effect on ectopic arrhythmias of supraventricular origin is somewhat conflicting, as shown by failure of the drug to convert auricular fibrillation of long standing to sinus rhythm, whereas it was effective when the arrhythmia was of the paroxysmal type, and in 3 out of 4 instances auricular ectopic contractions were abolished; also, in 1 patient with paroxysmal auricular tachycardia the drug appeared to have sensitized the carotid sinus reflex mechanism (co-incidence?).

Of its effectiveness in abolishing arrhythmias of ventricular origin, however, there would appear to be little doubt. Certainly the evidence appears to be conclusive with regard to ectopic contractions, inasmuch as they were abolished, even though temporarily, in 12 out of 14 patients. The response in 2 of the cases of ventricular tachycardia was dramatic and conclusive; in one of the others the patient was so near death at the time of administration of the drug that it is probable that nothing could have saved her; in the remaining patient there is a question as to whether death resulted from the drug or whether the ectopic rhythm might have been abolished had a larger dose been given and injected more rapidly. Experience with the 2 surviving patients leads to the belief that the latter may be a possibility.

No attempt was made as a specific objective to determine the duration of the antiarrhythmic effect. However, it is obvious that in many instances, at least, it was of relatively short duration. It is probable that, where a prolonged effect is desired, the oral route may be preferable, except in instances of those ectopic tachycardias where "time is of the essence", since sinus rhythm, once restored, usually persists.

Procaine amide has, then, a very definitely beneficial effect in abolishing certain cardiac arrhythmias. But this effect is by no means an unmixed blessing when the drug is given by the intravenous route. While unpleasant subjective sensations are the exception rather than the rule, nevertheless, objective signs occur which can be regarded only as undesirable, even though they were apparently not serious in the patients reported on here, with one possible exception. The blood pressure fell in nearly every instance, sometimes to a very pronounced degree; the pulmonary arterial pressure usually fell significantly, the mean circulation time usually increased, and the cardiac output usually decreased; and intraventricular conduction was practically always impaired, sometimes to a very marked degree. Certainly these changes can be regarded only as indicating an adverse effect on the cardiovascular system. No attempt was made to correlate the degree of these changes with either the size of the dose or the speed of injection, but the distinct impression was gained that the latter is the more important factor. It is concluded that, for maximum safety, it is preferable not to exceed a rate of 100 mg. per minute, except where life appears to depend on a matter of minutes.

Two questions naturally follow: Is one justified in using procaine amide by the intravenous route in the treatment of cardiac arrhythmias, in view of the toxic effects that follow? If so,

under what conditions should it be used? Since other reports[1] indicate that the drug is effective when given orally, it would seem reasonable that when it is considered advisable to employ it for the elimination of ectopic contractions (and these instances must represent a very small minority of all the patients in whom this arrhythmia occurs) it had best be given by the oral route, for toxic effects, though apparently present in many instances, are reported to be of a relatively mild degree. Even in many instances of paroxysmal rapid heart action, including the very serious ventricular tachycardias, there is evidence that the drug is often effective when given by mouth. Even though no deaths or serious toxic effects could be definitely ascribed to it in the patients here reported, yet the very definite deleterious effects observed electrocardiographically and hemodynamically would preach caution and argue potently against its indiscriminate and unrestricted use by the intravenous route. Nevertheless, its margin of safety still appears to be considerable and therefore it may be employed without hesitation in instances of ventricular tachycardia where time appears to be of the utmost importance, and of other types of paroxysmal rapid heart action which have failed to respond to its oral administration and to other measures. And, of course, during anesthesia, where the oral route is impractical, it will undoubtedly find a major field for its use with comparative safety, provided that the rate of injection does not exceed 100 mg. per minute.

Summary. 1. Procaine amide (Pronestyl) in doses of 200 to 2000 mg. was given intravenously to 41 patients with a total of 51 cardiac arrhythmias, and to 11 with normal sinus rhythm.

2. In general, those arrhythmias of supraventricular origin failed to be influenced by the drug, excepting auricular ectopic contractions and recent (paroxysmal) auricular fibrillation.

3. Ventricular ectopic contractions were abolished in 12 out of 14 instances. Ventricular tachycardia was abruptly stopped in 2 out of 4 patients; the remaining 2 died, one being in extremis at the time, while the death of the other may have been either due to the drug or in spite of it, and conceivably might have been averted by a larger dose administered more rapidly.

4. Subjective toxic effects were the exception rather than the rule, but objective toxic effects were the rule rather than the reverse. The latter consisted of fall in peripheral blood pressure and in pulmonary arterial pressure, decrease in cardiac output, and increase in circulation time and intraventricular conduction times. No serious toxic effects were observed except possibly in 1 of the 2 fatal cases of ventricular tachycardia.

5. It is concluded that the intravenous route of administration of procaine amide should be reserved chiefly for those patients with paroxysmal rapid heart action who are in immediate danger of death, or in whom the oral administration of procaine amide or other measures have failed, and for patients under anesthesia.

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HEMODYNAMIC CHANGES FOLLOWING PROCAINE AMIDE ADMINISTERED INTRAVENOUSLY*

By Robert L. McClendon, M.D.

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Procaine, in the form of the hydrochloride, has been known for many years to have an antiarrhythmic action on the ventricular muscle. It has been used quite generally for that purpose by anesthetists. Hazard[2] found that, like quinidine, it prolonged the refractory period and depressed muscular irritability. The amide derivative of procaine was investigated by Mark *et al.*[5], who found that its properties were similar to those of the hydrochloride but of lesser degree, because of its slower though more sustained action. Both forms of procaine have a definite hypotensive effect. The amide also produces electrocardiographic changes[3,4], the most striking of which is a prolongation of the QRS complexes.

So far as can be determined, no observations have been reported on the effect of procaine amide on the fundamental hemodynamic functions such as cardiac output, velocity of blood flow, and others. Consequently, as a supplement to a clinical study of the antiarrhythmic effects of the drug in 41 patients exhibiting 51 ectopic rhythms[3], an investigation of these fundamental hemodynamic effects was instituted in 10 individuals, some with normal hearts, some with heart disease.

Clinical Material and Methods. Of the 10 patients (see Figures), Cases 4, 5 and 10 had no evidence of heart disease. Case 3 had no evidence of heart disease excepting for recurrent attacks of (paroxysmal) nodal tachycardia. Cases 2 and 7 had hypertensive-arteriosclerotic heart disease. Cases 1 and 8 had rheumatic heart disease. One had auricular fibrillation and had hypertension thought to be secondary to a right renal artery embolus. Case 6 had congenital (from history) bundle branch block, but no other evidence of heart disease. Case 9 had cor pulmonale secondary to pulmonary fibrosis.

All were on maintenance doses of digitalis excepting the 3 without evidence of heart disease (Cases 4, 5, and 10) and the patient with congenital bundle branch block (Case 6) who had ventricular bigeminy.

All of the patients were fasting and in the recumbent position when the studies were carried out. In each one, cardiac catheterization was performed by the method of Cournand–Ranges[1], the catheter being advanced to the bifurcation of the pulmonary artery whenever possible. Arterial samples were collected from a cannula inserted into the radial artery. Pressures were recorded by a Sanborn electromanometer, mean pressures being determined by electrical integration.

The following measurements, determinations, and calculations were made:

1) Heart rate and rhythm were recorded electrocardiographically.
2) Right atrial, right ventricular, pulmonary arterial, radial arterial, and venous pressures were measured by direct recording.
3) Cardiac output was calculated by a modification (intracardiac catheter in-

* Supported in part by a grant from the National Heart Institute of the U. S. Public Health Service.

jection) of the dye-injection method of Hamilton, Moore, Kinsman, and Spurling[6]. The calculation was based on a modification of Stewart's formula.

4) Appearance and mean circulation times were measured by the method of Hamilton, Moore, Kinsman, and Spurling[6].

5) "Pulmonary Blood Volume" was calculated by Stewart's method.

monary arterial pressures within a range of ± 5 mm. Hg. Consequently, variations from the control figures exceeding those limits were considered to be significant.

In every case, *Control* studies were first carried out prior to the injection of the drug. Then, while the catheter and cannula remained in place, procaine amide was injected intravenously at a rate not exceeding 100 mg. per minute, an electrocardiogram being recorded continuously and the blood pressure taken in the usual manner at frequent intervals. Immediately following the end of the injection, the hemodynamic studies were repeated (*Peak* Effect), and again 30 minutes later (*Recovery* Stage). A total of 1000 mg. procaine amide was given to every patient, except in Case 1 in which 500 mg. were given.

TABLE 1.—MEASUREMENTS OF HEMODYNAMIC FUNCTIONS IN 10 PATIENTS GIVEN PROCAINE AMIDE INTRAVENOUSLY

Case No. and Diagnosis		*Heart Rate min.*	*Mean Pressure*					**Mean Circulation Time sec.*
			Right Atrium mm. Hg	*Right Ventricle mm. Hg*	*Pulmonary Artery mm. Hg*	*Radial Artery mm. Hg*	*Venous mm. H2O*	
1.	Control	68	4.8			76.0	104	21.2
Rheumatic	Peak	54				57.5		24.0
Heart disease	Recovery	58	6.6			68.0		23.4
2.	Control	60		8	10	85	80	18.6
Hypertensive-	Peak	60			8	75		20.0
Arteriosclerotic	Recovery	60			11	75		18.0
Heart disease								
3.	Control	75	2.5		17	43	94	12.6
No heart disease	Peak	72			14	47		12.6
(Paroxysmal nodal tachycardia)	Recovery	72			22	62		15.0
4.	Control	70			9	75	105	18.8
No heart disease	Peak	76			6	60		20.2
	Recovery	78			4	75		18.2
5.	Control	70	7		17	92	75	12.4
No heart disease	Peak	80			15	80		12.0
	Recovery	74			14	90		12.8
6.	Control	90	4.6		14	105	143	16.0
Congenital bundle	Peak	102			12.75			19.6
branch block	Recovery				10.2			
7.	Control	60	2.2	7.5		110	97	21.2
Hypertensive-	Peak	64		12.0		75		26.3
Arteriosclerotic	Recovery	56		11.0		45		29.0
Heart disease								
8.	Control	105	10	56	70	125	175	23.2
Rheumatic heart	Peak	120			62.5	110		28.6
disease with auricular fibrillation	Recovery	105	8		62.5	115		28.5
9.	Control	82	2.5		37.0	75	160	11.9
Cor pulmonale	Peak	90			33.0	75		12.9
	Recovery	85	5		38.0	60		13.0
10.	Control	60	2		17.0	75	95	14.0
No heart disease	Peak	65			20.0	85		13.6
	Recovery	65			22.0	75		14.5

6) Peripheral resistance was calculated from the formula:

$$\text{Resistance} = \frac{\text{Pm} \times 1332}{\text{C. O.}},$$

where Pm = mean radial arterial pressure in mm. of Hg., 1332 is a constant, and C. O. represents cardiac output in cc. per second. Results are expressed in absolute units.

Previous experience with these techniques leads to the conclusion that cardiac output determinations on the same individual under identical circumstances are reproducible within a range of ± 10%, and mean pul-

Results. The results of the direct measurements of heart rate, intracardiac and intravascular pressures, and mean circulation time are recorded in

Table 1. The results of the calculations of cardiac output, pulmonary blood volume and peripheral resistance are shown in Table 2. The changes in the radial arterial pressure are shown graphically in Fig. 1, those in the pulmonary arterial pressure in Fig. 2, those in the mean circulation time in Fig. 3, and those in the cardiac output in Fig. 4.

TABLE 2.—CALCULATIONS OF HEMODYNAMIC FUNCTIONS IN 10 PATIENTS GIVEN PROCAINE AMIDE INTRAVENOUSLY

Case No.		*Cardiac Output L./min.*	*Pulmonary Blood Volume L.*	*Peripheral Resistance dynes/sec.²*
1.	Control	3.5	1.24	1731
Rheumatic	Peak	3.1	1.24	1483
Heart disease	Recovery	3.6	1.40	1514
2.	Control	4.8	1.48	1411
Hypertensive-	Peak	3.05	1.01	1929
Arteriosclerotic heart disease	Recovery	5.1	1.53	1181
3.	Control	3.5	0.74	981
No heart disease	Peak	3.6	0.75	1048
	Recovery	3.3	0.82	1367
4.	Control	5.7	1.78	1025
No heart disease	Peak	5.4	1.83	884
	Recovery	5.1	1.56	1164
5.	Control	8.75	1.81	821
No heart disease	Peak	8.05	1.61	801
	Recovery	7.0	1.50	1024
6.	Control	6.45	1.72	1302
Congenital	Peak	4.8	1.57	1749
heart disease	Recovery			
7.	Control	3.5	1.23	2522
Hypertensive-	Peak	2.8	1.23	2143
Arteriosclerotic heart disease	Recovery	2.95	1.43	1223
8.	Control	4.15	1.71	2403
Rheumatic	Peak	3.2	1.51	2785
heart disease (auricular fibrillation)	Recovery	3.4	1.59	2751
9.	Control	8.4	1.66	714
Cor pulmonale	Peak	8.43	1.81	712
	Recovery	7.9	1.71	607
10.	Control	6.1	1.43	979
No heart disease	Peak	6.7	1.51	1020
	Recovery	6.0	1.45	1132

Heart Rate. In 7 patients there was a slight increase in heart rate, averaging 9 beats per minute. In the other 3 there was no significant change.

Mean Radial Arterial Pressure (Fig. 1). In 6 of the 9 patients in whom this was measured, there was a significant fall at the time of Peak Effect, the greatest drop occurring in one of the patients having hypertensive-arteriosclerotic heart disease; in this patient the pressure was even lower 30 minutes later. In 4 of the 6 patients the hypotensive effect was still evident 30 minutes later. In 2 patients there was a slight rise in radial arterial pressure and in 1 there was no appreciable change at the end of the injection, although the pressure was considerably lower 30 minutes later.

Mean Intracardiac Pressure. Too few measurements were made of intra-

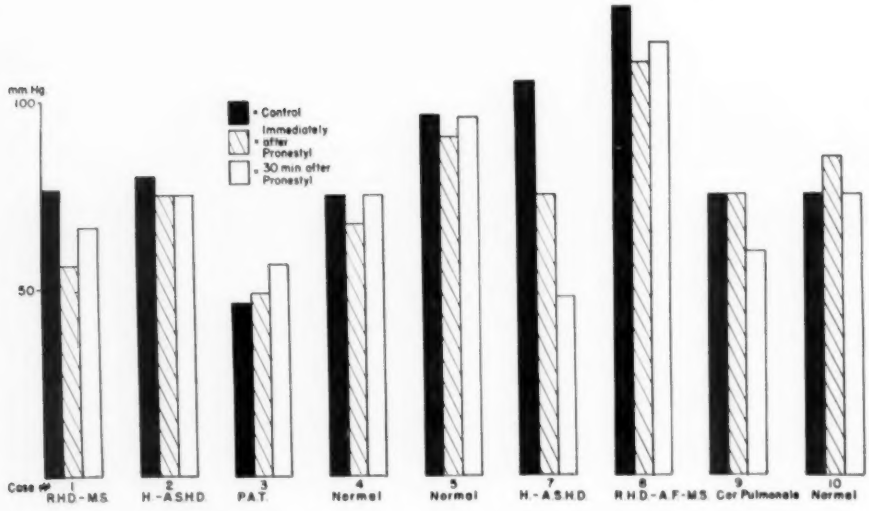

FIG. 1.—Effect of procaine amide on mean radial artery pressure. (In this and succeeding figures, the cases are numbered in chronological order. R.H.D.: Rheumatic Heart Disease; H.-A.S.H.D.: Hypertensive Arteriosclerotic Heart Disease; P.A.T.: Paroxysmal Auricular Tachycardia (actually nodal tachycardia; see text); A.F.: Auricular Fibrillation; M.S.: Mitral Stenosis.)

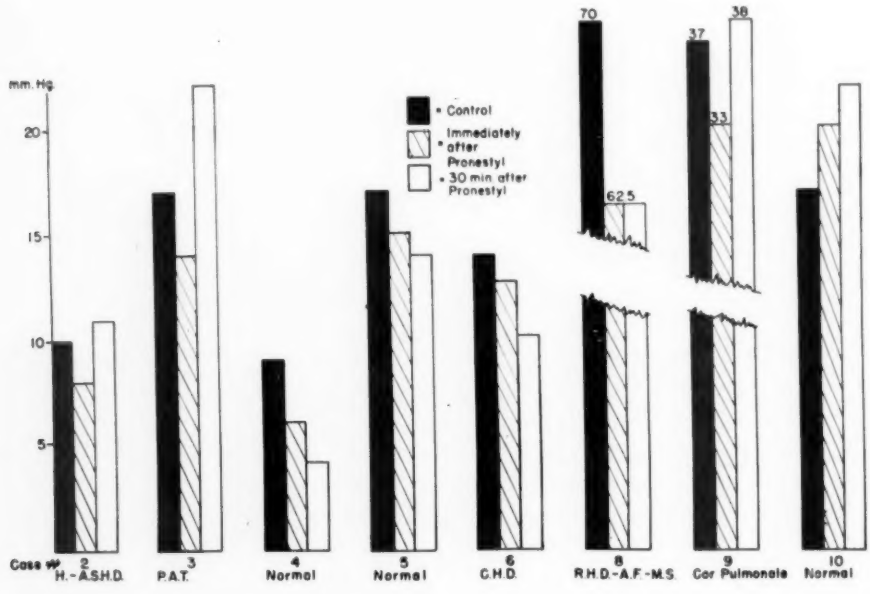

FIG. 2.—Effect of procaine amide on mean pulmonary artery pressure. (C.H.D.: Congenital Heart Disease (Bundle Branch Block). Otherwise abbreviations as for Figs. 1 and 2.)

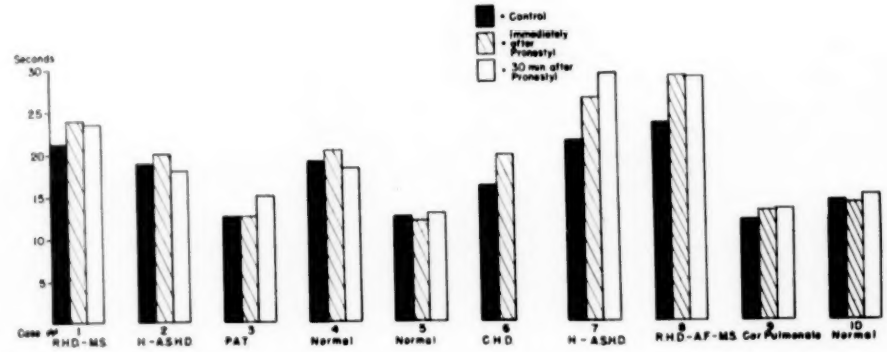

FIG. 3.—Effect of procaine amide on mean circulation time. (Abbreviations as for Figs. 1 and 2.)

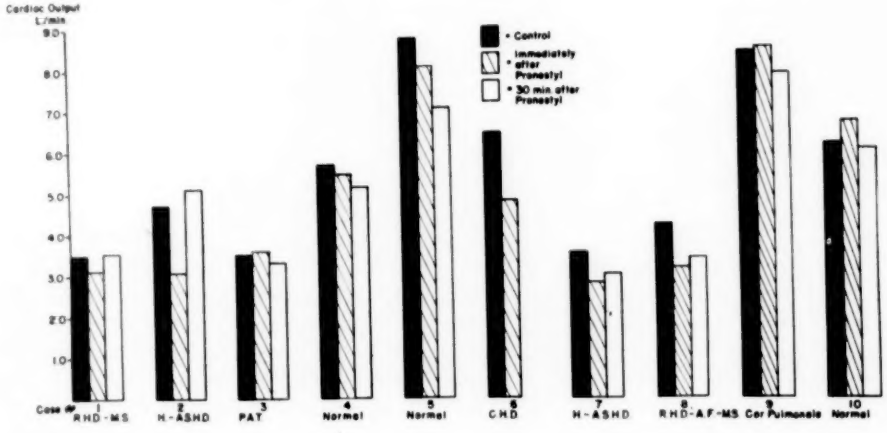

FIG. 4.—Effect of procaine amide on cardiac output. (Abbreviations as for Figs. 1 and 2.)

atrial and intra-ventricular pressures from which valid conclusions could be drawn.

MEAN PULMONARY ARTERIAL PRESSURE. In 7 of the 8 patients in whom this was measured (Fig. 2), there was a fall, being to a significant degree in 5 of them. Two of these had abnormally high pressures in the beginning, 1 patient having mitral stenosis and the other cor pulmonale. In 3 the pressure had returned to and beyond the control level 30 minutes later; in 3 it had fallen even lower by this time. In the remaining one (whose heart was normal) it rose after the injection; it had risen still further 30 minutes later.

MEAN CIRCULATION TIME (Fig. 3). This function was determined in 10 patients. In every patient the mean circulation time and appearance time were prolonged over the control value; in 3 these had returned to the control values at the end of the observation period.

PERIPHERAL RESISTANCE. No consistent response was observed. However, there was usually a reciprocal relationship with cardiac output: in most patients in whom a fall in cardiac output occurred there was an increase in peripheral resistance.

PULMONARY BLOOD VOLUME. In 4 patients the pulmonary blood volume decreased; in 3 it increased; and in 3 there was no change.

CARDIAC OUTPUT. (Fig. 4). In 5 patients the cardiac output was significantly decreased at the time of Peak Effect; in 1 there was an increase of borderline significance, in the remaining 4 there was no significant change. Three of these 4 patients had normal hearts, while the patient with a borderline increase also was 1 of the 4 normals. In 1 of the normals the cardiac output 30 minutes later had fallen significantly below the control level. In 3 of the 5 who had a significant fall at the end of the injection, the output was still significantly low 30 minutes later, but in the other 2 it had returned to the control level or above at the time of this observation. (In 1 no determination was made during the Recovery Stage.)

Discussion. In an attempt to evaluate the hemodynamic actions of procaine amide in this group of patients, only the immediate effects of the drug were studied. It is recognized that the figures for cardiac output obtained by the dye-injection method may not represent true absolute values, for so far no practical method has been devised which will give truly accurate figures in the human. There are probably errors in the method which are due to recirculation of dye. Nevertheless, these errors are all in the same direction and it is reasonable to believe that the changes in the cardiac output determinations which are obtained on the same individual reflect what is actually occurring in the heart's dynamics. Hence an increase or a decrease in the figure is considered to be significant, even though it may be argued that it may not be strictly quantitative.

The so-called Pulmonary Blood Volume figures are certainly open to some question as to their significance. They are presented here simply for the record and without any attempt to draw conclusions from them.

One other factor possibly influencing the results is the apprehension of the patient, due to the fact that the method requires cardiac catheterization and cannulization of an artery. However, such psychic influences tend to accelerate the velocity of blood flow, rather than to retard it as usually was the case here. Furthermore, in a large number of other patients in whom the identical procedure has been carried out without the introduction of any other known variable factor, the cardiac output figure has generally been reproducible within $\pm$ 10% of the initial level. Therefore, the likelihood that psychic factors influenced the results appreciably is not great.

From the above data, it appears that one of the more important effects of the intravenous administration of the drug is a reduction in cardiac output. It is well known that the dynamics of the circulatory system depends upon the discharge volume of each ventricle, the elasticity and peripheral resistance of the peripheral vessels, and the viscosity and volume of circulating blood. The output of the heart depends (among others factors) upon the efficiency of its contractions and upon the venous return. If a decrease in venous return were the dominant factor in the reduced cardiac output that usually followed the administration of procaine amide in these patients, there should have been an associated rise in peripheral resistance with an increase in mean radial arterial pressure. This was not usually the case, for in those cases where the peripheral resistance did increase, the radial artery pressure nearly always fell. It would appear, then, that the fall in cardiac output

was the result of a primary myocardial action.

From the evidence presented, the effect of procaine amide on the peripheral arteriolar bed is variable. The changes observed may represent a balance between a primary vasodilator effect upon arterioles or a reflex alteration secondary to a primary myocardial effect. The slowing of the rate of blood flow is consistent with either one. The decrease in pulmonary arterial pressure may be due to a dilatation of the pulmonary vascular bed, or to a redistribution in the entire vascular bed with a lowering of vascular resistance, or to a decrease in cardiac output.

These studies also suggest a rather important conclusion. It is rather striking that the patients with normal hearts showed no fall in cardiac output, whereas all of those with heart disease did. Moreover, the decrease in velocity of blood flow and in mean radial and pulmonary arterial pressures was definitely less marked than in those patients with diseased hearts. Furthermore, the clinical studies revealed less interference with intraventricular conduction in patients with normal hearts than in those with diseased hearts[3]. It is quite probable, therefore, that procaine amide has very definitely a greater deleterious myocardial action on diseased hearts than on normal ones, and that its harmful effects on the normal heart are comparatively mild. This is a point of the utmost clinical importance, since many of the arrhythmias for which the drug appears to be useful occur in apparently quite normal hearts. It is concluded, therefore, that caution should be especially observed in those patients whose hearts are known to be damaged, but that in normal hearts it is probably a comparatively safe drug.

Summary. 1) The immediate effects of intravenously administered procaine amide were studied by cardiac catheterization in 10 patients.

2) Procaine amide usually produced a fall in cardiac output, a decrease in blood flow through the pulmonary vascular bed, accompanied by a fall in pressure in the pulmonary artery, a fall in mean radial arterial pressure with variable changes in peripheral resistance, and significant slowing of the velocity of blood flow as measured by the dye-appearance and mean circulation times. These changes were most pronounced in patients with diseased hearts and least evident in those with normal hearts.

3) It is concluded that procaine amide has its major effect through a primary myocardial depressant action, although this response may be variable ranging from little or no effect on circulatory dynamics to a significant change in the peripheral arteriolar bed. It is probable that it is a comparatively safe drug in patients with normal hearts, but that it should be used cautiously in those with diseased hearts.

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QUINIDINE TREATMENT OF AURICULAR FIBRILLATION*

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The proper place of quinidine in the treatment of auricular fibrillation is still in a state of flux. Considerable fear has been built up about the serious dangers of this valuable drug. For this reason this study was undertaken to help clear up many of the common misconceptions in the use of this medication.

Analysis of Cases. To date 80 patients with auricular fibrillation have been carefully studied. Since this study was carried out in a Veterans Administration Hospital, all but 2 of the 80 patients were males. The age of the patients ranged from 28 to 88, the majority being in the sixth decade of life (see Table 1). The exact duration of the auricular fibrillation was unknown in most instances, ranging from a few days to 30 years. It is estimated that the auricular fibrillation had existed for many years in the majority of the patients.

TABLE 1.—AGE DISTRIBUTION IN 80 CASES OF AURICULAR FIBRILLATION

Age Group	*No. of Cases*
20–29	1
30–39	4
40–49	8
50–59	34
60–69	21
70–79	11
80–89	1

Etiology. The type of heart disease responsible for the auricular fibrillation has been classified as: 1) degenerative heart disease, to include the arteriosclerotic and hypertensive group; 2) rheumatic heart disease, which has been sub-divided into: a) mitral lesions or combined mitral and aortic lesions, and b) pure aortic lesions; 3) thyrotoxic heart disease; and 4) unclassified heart disease. This last group includes those patients who could not be classified into any of the above 3 groups and included patients with "idiopathic" auricular fibrillation (4 cases), "chronic myocarditis" (1 case), luetic aortic insufficiency with auricular fibrillation (1 case), and possible amyloid heart disease (1 case). See Table 2 for further details.

TABLE 2.—ETIOLOGY IN 80 CASES OF AURICULAR FIBRILLATION

Type of Heart Disease	*No. of Cases*
Degenerative	44
Rheumatic (total)	25
Mitral (or mitral plus aortic)	22
Aortic	3
Thyrotoxic	4
Unclassified	7

* Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the author are the result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

It must be understood that the etiological diagnosis was in most instances made on clinical evaluation. It therefore cannot be considered 100% accurate. In some instances there was a difference of opinion as to the etiological diagnosis, but a final decision was reached after repeated careful physical examinations correlated with electrocardiographic and roentgenographic findings.

Cardiac Enlargement. The degree of cardiac enlargement was based on the actual size of the heart as measured on a standard chest roentgenogram in comparison with the predicted measurement. The degree of cardiac enlargement has been classified as none, slight, moderate, and marked (see Table 3).

TABLE 3.—CARDIAC ENLARGEMENT IN 80 CASES OF AURICULAR FIBRILLATION

	No. of Cases	%
None	14	17.5
Slight	17	21.2
Moderate	28	35.0
Marked	21	26.3

Emboli. The data used in the determination of the number of embolic phenomena occurring during the course of the auricular fibrillation and before attempted conversion with quinidine include those cases in which obvious embolic episodes were observed and those in which the history was definitely indicative of such. In many instances there was suggestive evidence by history of embolization, but since this was not too conclusive, these were not included. Of the 80 patients studied there were 22 instances of embolic phenomena, that is, an incidence of 27.5%. Of these, 8 (10%) were pulmonary emboli and 14 (17.5%) were systemic emboli. Analyzing these in relation to the type of heart disease, 45.5% (10 of the 22 embolizations) occurred in the Rheumatic group, 40.9% (9 of 22) in the Degenerative group, and 13.6% (9 of 22) in the Unclassified group. (See Table 4).

It is the present policy to administer anti-coagulants to all patients with evidence of recent embolic phenomena. This therapy is maintained for approximately 14 days prior to administration of quinidine and is maintained during quinidine therapy until the rhythm is converted or until quinidine is discontinued. This regimen is carried out in the belief that recently formed auricular thrombi may be more easily dislodged than older thrombi which may be more firmly adherent to the auricular endocardium. Thus a 2-week period of anti-coagulant therapy may prevent the formation of new thrombi and thus may minimize the danger of embolism following conversion. Whether this regimen should be followed in all patients to be treated with quinidine cannot be answered at this time.

Congestive Heart Failure. The majority of the patients studied were in

TABLE 4.—EMBOLI DURING FIBRILLATION IN 80 CASES OF AURICULAR FIBRILLATION

	Rheumatic Disease	*Degenerative Disease*	*Unclassified*	*Total*	%
Pulmonary	5	2	1	8	10
Systemic	5	7	2	14	17.5
Total	10	9	3	22	27.5
% of Emboli	45.5	40.9	13.6		

congestive heart failure at the time of admission. These were first treated with digitalis, oxygen, salt restriction and mercurial diuretics, as indicated. In some instances the congestive failure did not respond to the above measures. The results following quinidine therapy are given below.

Bundle Branch Block. Of the 80 patients studied, 9 had electrocardiographic evidence of bundle branch block. Of these 9, 4 had right bundle branch block (QRS = 0.12 to 0.14 sec.), 2 had left bundle branch block (QRS = 0.12 to 0.14 sec.), and 3 had incomplete right bundle branch block (QRS = 0.1 sec.). All of the above received quinidine.

Method of Quinidine Administration. The patient is first given a dose of 0.2 gm. to test for sensitivity. In the early part of this study most patients were then started on a dosage of 0.2 gm. every 2 hours for 5 or more daily doses. The individual dose was then increased at 1- to 2-day intervals to 0.4 gm., 0.6 gm., 0.8 gm., 1.0 gm., and 1.2 gm. On this increasing dosage, high blood quinidine levels were rapidly obtained, and although serious toxic effects were rarely encountered, many patients were quite uncomfortable because of dizziness, nausea, vomiting, and diarrhea. With the more recent studies with respect to quinidine excretion and quinidine blood levels[5], patients are now started on a dosage of 0.2 gm. 4 times daily. This is maintained for 3 days. If conversion does not occur, the dose is raised to 0.4 gm. 4 times daily for 3 days, and then, if necessary, to 0.6 gm., 0.8 gm., 1.0 gm., and 1.2 gm. 4 times daily, each dose being maintained for at least 3 days. Only when reversion does not occur on a dose of 1.2 gm. 4 times daily is the schedule of 2-hourly doses resorted to, that is, 1.2 gm. every 2 hours for 5 or more daily doses. As a rule a total daily dose of 6.0 gm. was not exceeded, but in a few patients a total of 7.2 gm. was given.

The patient is carefully observed during the above treatment. Symptoms of dizziness, nausea, vomiting, and diarrhea are not infrequent and are not, in themselves, considered a contraindication to continuation of therapy. Blood pressures are taken before each dose of quinidine. Any appreciable drop in blood pressure (20 mm. or more of diastolic pressure) is considered an indication for discontinuing quinidine, at least temporarily. Electrocardiograms (V_1 strips) are taken twice daily. It has been our experience that a definite diagnosis of the type of rhythm cannot always be determined clinically. An irregular auricular flutter will simulate an auricular fibrillation and a 2:1 or 4:1 flutter, or nodal rhythm can simulate a regular sinus rhythm clinically.

Results. Conversions with Quinidine. (See Table 5). Of the 80 cases studied, successful reversion to a regular sinus rhythm was obtained in 67 (83.8%). It is of further interest to analyze the percentage of reversion in relation to the type of heart disease.

TABLE 5.—CONVERSIONS TO NORMAL BEAT WITH QUINIDINE THERAPY

Type of Heart Disease	*No. of Cases*	*No. of Conversions*	*%*
Degenerative	44	44	100
Rheumatic, total	25	13	52
Mitral (or mitral plus aortic)	22	10	45.5
Aortic	3	3	100
Thyrotoxic	4	4	100
Unclassified	7	6	85.7
Total	80	67	83.8

1. *Degenerative Group.* It is noteworthy that in all 44 (100%) patients with arteriosclerotic and/or hypertensive cardiovascular disease reversion occurred. This result is possibly fortuitous and probably does not mean that in every such case will the rhythm be converted to normal. However, it does indicate the very high incidence in which reversion will occur. As a rule very high doses of quinidine were not necessary; in the average patient reversion occurred on 0.4 to 0.6 gm. 4 times daily.

2. *Thyrotoxic Group.* In all 4 patients in this group reversion followed

treatment. All patients were initially rendered euthyroid with propylthiouracil and iodides before quinidine was given. However, it will be of interest to cite one of the above patients who returned 18 months after his first hospitalization with recurrent hyperthyroidism (BMR [basal metabolic rate] = 37) and recurrent auricular fibrillation. Because he had been unsuitable for surgery he had been maintained on propylthiouracil (150 mg. per day) and quinidine (0.4 gm. 4 times daily) for 15 months. He remained euthyroid and in a regular sinus rhythm. Both medications were then discontinued and 3 months later he was again hyperthyroid and had auricular fibrillation. While still hyperthyroid he was given quinidine, 0.4 gm. 4 times daily, and the rhythm reverted to normal on the 3rd day. This raises the question of the necessity of waiting until the patient is euthyroid before attempting conversion. One such case cannot be used to draw any definite conclusion, but it probably indicates that conversion can be accomplished while the patient is hyperthyroid, but that the result may be more easily obtained at a euthyroid level.

3. *Rheumatic Group.* Conversion was effected in 13 of the 25 patients with rheumatic heart disease (52%). In all 3 patients with aortic valvular involvement alone, reversion followed treatment. However, of the 22 patients with involvement of the mitral valve (mitral stenosis) the beat was converted to normal rhythm in 10 (45.5%). It is therefore apparent that this is the one group of patients in whom conversion is most difficult, but this must not be considered an indication for not making the attempt. Even though the possibility of conversion is slightly under 50%, it is still highly desirable.

4. *Unclassified Group.* Of the 7 patients in this group conversion was accomplished in 6 (85.7%). This group is so small and consists of such miscellaneous types of heart disease that no further conclusions can be drawn.

TABLE 6.—CARDIAC ENLARGEMENT IN 80 CASES OF AURICULAR FIBRILLATION

	No. of Cases	*No. of Conversions*	*%*
None	14	14	100
Slight	17	12	70.6
Moderate	28	24	85.7
Marked	21	17	80.9

AURICULAR FLUTTER. This rhythm was detected electrocardiographically in 52 of the 80 cases (65%). This is readily understandable in the light of Sherf's original work[4], as later confirmed by Prinzmetal[3]. This matter has been discussed more thoroughly in a previous publication[2].

CARDIAC ENLARGEMENT. (See Table 6.) There was no appreciable difference in conversion rate in relation to the degree of cardiac enlargement. In those patients with moderate and marked cardiac enlargement, the conversion rates were 85.7% and 80.9%, respectively. A greater degree of cardiac enlargement did not make the conversion more difficult nor did it necessarily mean that higher doses of quinidine were required. In a few of the patients (reported in the following paragraphs) the cardiac size was reduced following conversion to a regular sinus rhythm.

CONGESTIVE FAILURE. Ten of the 80 patients with congestive failure were definitely improved both subjectively and objectively following conversion. The following are examples of such improvement.

CASE 1. J.C., a white male, age 71, had hypertensive cardiovascular disease, auricular fibrillation, marked cardiac enlargement, and right and left heart failure not controlled by

bed rest, oxygen, digitalis, salt restriction, and mercurial diuretics. Following conversion, the patient became fully compensated and became ambulant.

CASE 2. W.S., a white male, age 28, had rheumatic heart disease, auricular fibrillation, marked cardiac enlargement, and mitral stenosis. He remained in chronic heart failure for weeks in spite of bed rest, digitalis, salt restriction, and mercurial diuretics. Following conversion, he became compensated for the first time in his present illness.

EMBOLI. As mentioned above, 27.5% of the total 80 patients had definite evidence of embolization while in auricular fibrillation. During the period of quinidine administration, three patients showed evidence of embolic phenomena. These case histories are briefly reviewed:

CASE 3. F. P., a white male, age 39, had rheumatic heart disease, auricular fibrillation, and mitral stenosis. Shortly after admission and while still fibrillating the patient developed an embolic occlusion of the right brachial artery which was relieved by embolectomy. Two weeks following this he was started on quinidine therapy, after receiving anti-coagulant therapy for the previous 14 days. His beat was converted to a regular sinus rhythm on the second day of quinidine administration. Six hours following conversion he developed a pulmonary infarction and auricular fibrillation recurred. Quinidine was maintained in increasing doses and on the 12th day of quinidine therapy the beat again reverted to normal sinus rhythm. Since then (9 months later) the rhythm has remained normal and the patient has had no further embolic episodes. He takes a maintenance dose of 0.4 gm. 4 times daily.

Comment. This patient had an embolic episode shortly before conversion and it is possible that the second embolic episode may have occurred without reversion. Yet, for the purpose of this study, this must be classified as an embolus occurring with quinidine conversion.

CASE 4. P. F., a white male, age 58, had arteriosclerotic heart disease with auricular fibrillation, no failure, and no cardiac enlargement. The beat reverted to normal on the 3rd day of quinidine therapy. Four hours after regular sinus rhythm was established, the patient developed a motor aphasia with no other neurological findings. This disappeared completely in 48 hours. It most likely represents an embolus to the "motor aphasia center" of the brain.

CASE 5. C. F., a white male, age 70, had arteriosclerotic heart disease with auricular fibrillation, congestive failure which responded to digitalis and salt restriction, and marked cardiac enlargement. On the 2nd day of quinidine therapy the patient developed a nodal rhythm with retrograde P waves. Quinidine was immediately discontinued and the nodal rhythm persisted for the next 48 hours (the 3rd and 4th days after quinidine therapy was begun). On the 5th day a regular sinus rhythm was established (quinidine still being withheld). Several hours after onset of the regular sinus rhythm the patient developed a left hemiplegia which probably was not embolic in origin. The hemiplegia has persisted for an 8 months' follow-up period. The patient has been maintained in regular sinus rhythm with a maintenance dose of quinidine of 0.2 gm. 4 times daily.

BUNDLE BRANCH BLOCK. As stated above, 9 patients in this series had bundle branch block (6 complete, 3 incomplete). All patients received quinidine in routine dosage. In no instance was there any evidence of an increase in the intraventricular conduction time during administration of quinidine. This does not imply that widening of the QRS interval may not occur with a bundle branch block. However, it does indicate that the presense of bundle branch block, in itself, does not contraindicate the use of quinidine.

MAINTENANCE DOSE. Following conversion of the beat to a regular sinus rhythm, all patients were placed on a maintenance dose which was less than the dosage given at the time of conversion. No definite dosage schedule can be given, since in some instances the individual maintenance dose can be determined only by trial and error. However, in general, those patients in

whom the rate was converted to normal with a dose of 0.4 gm. 4 times daily have been satisfactorily maintained on 0.2 gm. 4 times daily. Those in whom the rate was converted to normal with a dose of 0.6 to 0.8 gm. 4 times daily have been maintained on 0.4 gm. 4 times daily. In some instances in which much higher doses were necessary for conversion, the patients have been maintained on 0.6 gm. 4 times daily. Some of these patients have now been followed for 2 years, and there is no known instance of an untoward effect from any of the above schedules. It is not recommended that quinidine be discontinued following conversion on the assumption that the regular sinus rhythm will be maintained for an indefinite period without further quinidine. In our experience, auricular fibrillation promptly returns with discontinuation of the drug. The following case is an example of this and of the occurence of a complication of the recurrent fibrillation:

CASE 6. W. R., a white male, age 48, first entered the Oakland Veterans Administration Hospital in March, 1948, with the finding of rheumatic heart disease, mitral stenosis, aortic stenosis and insufficiency, auricular fibrillation, and congestive heart failure. The heart was moderately enlarged. The failure responded completely to digitalis and salt restriction. The heart beat was then converted to normal sinus rhythm with quinidine and the patient was discharged from the hospital on a maintenance dose of 0.1 gm. of digitalis leaf once daily and 0.2 gm. of quinidine 4 times daily. A regular sinus rhythm was maintained up to June, 1949, when quinidine was discontinued by his private physician. The patient noted the return of an irregular pulse within the next month. He re-entered this hospital in September, 1950, following the sudden onset of a left hemiplegia while active. The rhythm was auricular fibrillation. The beat was again converted to normal with quinidine. Had the patient continued treatment with the quinidine at all times, it is more than likely that the hemiplegia, which was undoubtedly embolic, would not have occurred.

Toxic Effects of Quinidine. UNTOWARD SYMPTOMS. Many of the patients receiving quinidine complain of nausea, vomiting, diarrhea, dizziness, tinnitus, and weakness. As a rule these symptoms are of mild to moderate severity and in themselves are not a contraindication to continuation of the therapy. The use of phenobarbital, codeine, and paregoric are of value in controlling these symptoms. Rarely do they reach such severity as to require discontinuation of the quinidine. In this series it was necessary to stop the medication because of these symptoms in 2 patients. One patient was receiving 6.4 gm. per day and the other, 4.8 gm. per day at the time quinidine was discontinued.

FALL IN BLOOD PRESSURE. This is a definite indication for discontinuation of therapy. A drop of 20 mm. or more in the diastolic pressure should be taken as a warning sign and quinidine discontinued. This by no means implies that further quinidine therapy is contraindicated. When the blood pressure returns to its former level, quinidine should again be started, but in doses lower than that which resulted in the blood pressure drop. In this study this was never observed as an isolated finding. It did occur in 2 patients who showed, in addition, electrocardiographic evidence of quinidine toxicity.

ELECTROCARDIOGRAPHIC ABNORMALITIES. *Auricular Flutter.* As has been mentioned above, this is merely an intermediary rhythm between auricular fibrillation and regular sinus rhythm and is definitely not a contraindication to continuation of quinidine.

Ventricular Ectopic Beats. The appearance of an occasional ventricular ectopic beat in a patient who showed no evidence of this prior to quinidine is not an uncommon finding. However, it should be considered as a warning sign and the patient observed very

carefully. As the drug is continued, the ventricular ectopic beats may increase in frequency, may appear in long runs, or an actual idioventricular rhythm may develop. The occurrence of the latter two rhythms is a definite indication for immediate discontinuation of quinidine. Here again it does not mean that quinidine is not to be given in the future. When the ventricular ectopic rhythm has disappeared, quinidine can again be administered but in smaller dosage than that which resulted in the abnormal rhythm. The following case is an example of such an abnormal rhythm.

CASE 7. E. M., a white male, age 38, had rheumatic heart disease, auricular fibrillation, and mitral stenosis. An electrocardiogram before quinidine therapy showed auricular fibrillation with a QRS time of 0.08 sec. On a dose of 3.0 gm. per day the rhythm was auricular flutter with an occasional right ventricular ectopic beat. The following day on a dose of 4.0 gm. per day the rhythm was auricular flutter with frequent right ventricular ectopic beats, occasionally occurring in runs. The next day while still on a dose of 4.0 gm. per day, the auricular flutter persisted but the ventricular rhythm was regular and all the ventricular complexes had the configuration of a left bundle branch block with a QRS time of 0.16 sec. Quinidine was discontinued. The QRS interval diminished to 0.08 sec. within the next 24 hours and the auricular flutter persisted for 48 hours before auricular fibrillation re-appeared (see Fig. 1).

Widening of QRS. An increase in the QRS interval of 25% or more is a definite indication for the immediate discontinuation of therapy. This merely means that the dose of quinidine is too high for that particular patient and does not indicate that conversion cannot result with smaller doses. Examples of such occurrences are as follows:

CASE 8. J. F., a white male, age 67, had "idiopathic" auricular fibrillation of 30 years' duration; initial QRS interval = 0.1 sec. On a dose of 6 gm. per day the auricular fibrillation persisted and QRS lengthened to 0.16 sec. On another occasion, on 5.0 gm. per day the QRS interval increased to 0.14 sec. with persistence of the auricular fibrillation. On both these occasions the blood quinidine level was quite high. Subsequently, on doses of 2.4 to 3.2 gm. per day, which resulted in much lower blood quinidine levels, a regular sinus rhythm was established with the QRS interval remaining at 0.1 sec.

CASE 9. R. C., a white male, age 71, had rheumatic heart disease with aortic stenosis and insufficiency and chronic congestive heart failure. An electrocardiogram revealed auricular fibrillation, left ventricular hypertrophy, and a QRS time of 0.11 sec. Blood pressure before quinidine was 190/82. On a dose of 4.0 gm. per day the patient became quite weak, dizzy, and nauseated. The blood pressure fell to 140/60. The electrocardiogram showed an auricular flutter with a widening of the QRS interval to 0.18 sec. Quinidine was discontinued. Seventeen hours later the rhythm was regular sinus with a QRS of 0.11 sec. Quinidine was then restarted and maintained at 0.4 gm. 4 times daily. The regular sinus rhythm was maintained with marked lessening in the degree of heart failure which previously had resisted all other therapeutic measures.

CASE 10. M. C., a white male, age 65, had arteriosclerotic heart disease, auricular fibrillation, and a QRS interval of 0.09 sec. On a dose of 5.0 gm. per day the auricular fibrillation persisted and the QRS interval lengthened to 0.16 sec. Quinidine was discontinued. Twenty hours later the rhythm was regular sinus with a QRS interval of 0.11 sec. Quinidine was again started in a maintenance dose of 0.4 gm. 4 times daily. The regular sinus rhythm was maintained and the QRS interval returned to 0.09 sec.

Auriculo-Ventricular Nodal Rhythm Occurring During Quinidine Therapy. This type of rhythm appeared in 6 patients (8.9%). In 2 of the 6 there was no electrocardiographic evidence of auricular activity and in the remaining 4 there was auricular activity as evidenced by retrograde P waves[6]. It is of interest to note that in all instances this rhythm occurred with higher levels of quinidine in the blood than those taken at the time of conversion to a

regular sinus rhythm; and that the auriculo-ventricular nodal rhythm was converted to regular sinus rhythm when the dose of quinidine was reduced or temporarily discontinued.

Auricular-Ventricular Dissociation. The presence of this rhythm in any patient, regardless of an associated auricular rhythm of fibrillation or flutter, is a definite contraindication to the use of quinidine. Likewise the development of such a rhythm during quinidine administration necessitates immediate discontinuation of the drug. This rhythm occurred in one case:

CASE 11. P. G., a white male, age 58, had hypertensive and arteriosclerotic heart disease, auricular fibrillation, chronic congestive heart failure, and marked cardiac enlargement. Digitalis was pushed but the ventricular rate could not be reduced below 120 per minute. Quinidine was then begun. After the patient had received 2.4 gm. of quinidine daily for 3 days, the electrocardiogram revealed a complete auriculo-ventricular dissociation with an auricular rate of 64 and a ventricular rate of 75. It was felt that this could be the result of too much digitalis, too

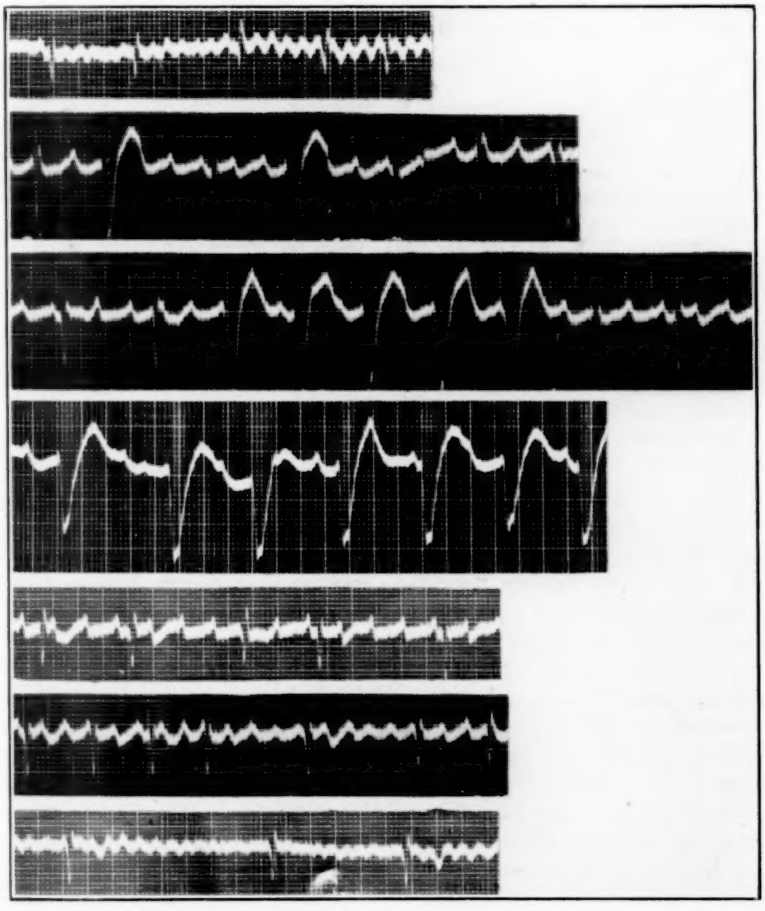

FIG. 1.—Case 5 (E.M.). The above electrocardiograms are all lead V_1. A, before quinidine therapy; B, 3rd day of quinidine therapy; C, 4th day of quinidine therapy; D, 5th day of quinidine therapy; E, F, and G, 1, 2, and 3 days, respectively, after discontinuation of quinidine therapy.

much quinidine, or a synergistic action of these 2 drugs. Therefore both drugs were discontinued. Twenty-four hours later the rhythm was regular sinus with a rate of 70. Digitalis leaf was then begun in a dose of 0.1 gm. per day and quinidine was given in a dose of 0.4 gm. 4 times daily. On these maintenance doses the regular sinus rhythm persisted with no untoward effects. Furthermore, the congestive heart failure cleared completely following conversion.

DEATH. One death occurred during quinidine administration. The case history is as follows:

CASE 12. H. P., a white male, age 52, had rheumatic heart disease, auricular fibrillation, mitral stenosis, and chronic congestive heart failure unresponsive to the usual therapeutic measures. The electrocardiogram revealed auricular fibrillation with a QRS interval of 0.12 sec. Quinidine therapy was then begun. The first day the patient received 2 gm. The second day he received 3.0 gm., the last dose being given at 3:00 p. m. At 4:00 p. m. the electrocardiogram revealed a 2:1 auricular flutter with a ventricular rate of 90. The QRS interval was 0.13 sec. No ectopic beats were present. At 4:30 p. m. the patient was again checked by his physician. The patient had no complaints and there was no change in the physical findings. The patient was found dead in bed at 5:00 p. m. The autopsy revealed mitral stenosis. There was no evidence of emboli. No obvious cause of death could be determined pathologically.

The cause of death in this patient is uncertain. It is possible that this represents a "central" effect on the respiratory and vasomotor centers or the sudden appearance of a ventricular fibrillation or asystole as a result of quinidine. Although similar deaths occur in cardiac patients who are not receiving quinidine, this case must be classified as a possible quinidine death.

Discussion. It is felt that many of the present concepts regarding quinidine must be revised. Unfortunately there is a feeling among many internists that quinidine is a highly toxic drug and that its use in conversion of auricular fibrillation is quite limited. Admittedly there are some potential toxic effects, but when the drug is used properly these can be reduced to a minimum. Are we to refrain from the proper use of this drug because it is not completely innocuous? If so, should we ever have used such valuable medications as salvarsan, emetine, or the sulfonamides?

Congestive heart failure and cardiac enlargement have been considered by some to contraindicate the use of quinidine for conversion of the beat in auricular fibrillation to normal. No such conclusion can be drawn from this study. In fact, to the contrary, the patient may have definite improvement in his compensation with actual reduction in heart size following conversion.

One major fear in the use of quinidine has been the possibility of embolism following conversion of the beat to a regular sinus rhythm. From this study it can be seen that the odds are approximately 7 to 1 in favor of a patient suffering an embolic episode while fibrillating as compared to the likelihood of occurrence at the time of conversion to a regular sinus rhythm.

It has been stated " . . . . its (quinidine) use in long-standing auricular fibrillation has for the most part been abandoned"[1]. This study has included many patients in whom the duration of the fibrillation was known to be from 2 to 10 years. The conversion results were quite excellent and there was no definite correlation between the untoward effects of the drug and the duration of the fibrillation. It was both surprising and gratifying to see the ease in which the beat of many of these long-standing fibrillators, especially those in the degenerative heart group, was converted to normal.

The advisability of the simultaneous use of digitalis and quinidine has been questioned by some. In this study practically all the patients did receive both

drugs. Furthermore, the majority of these patients were in congestive failure and therefore required digitalis. In only one instance (case P.G.) was there a possibility of toxicity from the synergistic action of the 2 drugs. It was pointed out that this patient had been over-digitalized in an attempt to reduce the ventricular rate. Certainly from a practical standpoint, with careful observation of the patient, there is no contraindication to the simultaneous use of these 2 drugs.

The appearance of toxic effects of quinidine in any given patient (fall in blood pressure, electrocardiographic abnormalities) is not a contraindication to future use of the drug in that patient. It merely is an indication that too high a dose had been given and does not indicate "sensitivity" of the patient. After the toxic manifestation has disappeared, the administration of quinidine in smaller doses can produce the desired effect.

There is no constant correlation between the time of administration of the drug, the expected height of the blood quinidine level, and the time of conversion. It was not uncommon to have the beat revert to a regular sinus rhythm, not at a period approximately 2 hours after the last dose of the day, at which time the blood level should be at its peak, but 6 to 12 hours later. Likewise, as has been illustrated above, high doses can produce toxic effects with maintenance of the auricular fibrillation and smaller doses can result in conversion.

Summary. 1. The results of treatment with quinidine in 80 patients have been reviewed.

2. An appeal is made to the internist for a revision of many of the older concepts regarding quinidine which should result in a more widespread, yet judicious, use of this valuable drug.

ADDENDUM: Since completion of the above study, 31 additional cases have been studied. Conversion was successful in 24, giving an over-all percentage of 82%. Of these additional cases, 20 were in the degenerative group and 11 in the rheumatic mitral group. Conversion was accomplished in 17 of the former group and 11 of the latter, resulting in an over-all conversion rate of 95.3% and 55.8%, respectively.

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SUCCESSFUL USE OF ACTH IN THE TREATMENT OF AGRANULOCYTOSIS DUE TO SULFADIAZINE

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THIS is a report of a case of agranulocytosis due to a toxic depression of bone marrow produced by a sensitivity reaction to sulfadiazine which was being administered for urinary bacteriostasis and pneumonia. The patient was treated with ACTH with rapid, remarkable, and at the time of this writing, complete recovery. It is realized that one case is hardly sufficient evidence on which to base the response of this condition to ACTH; however, because in this instance it was considered to be a life-saving procedure, it is being reported so that others who find this relatively rare and often fatal condition may give the medication further trial.

Many treatments have been suggested and none have been proved to be of definite value in changing the picture of the bone marrow or peripheral blood. Among those things suggested, and found of questionable value, are: pentnucleotide, folic acid, vitamin B_{12}, and blood transfusions. The present treatment is limited to discontinuing the use of the causative agent[1,3,5], administration of antibiotics to control infections, to which these subjects are very susceptible and have almost no resistance, and other supportive measures. This is frequently sufficient to effect recovery; however, the recovery is sometimes protracted, requiring a period of several weeks.

A review of the recent literature shows 2 medications to be frequent offenders in causing this disease. They are the antihistamines and the sulfonamides. Many other medications may cause the condition, and there are countless reports of these agents, among which are pyramidon, dilantin, and thiouracil. The first two mentioned are of particular significance because of their widespread and frequent usage.

Thorne and co-workers[4], in a recent publication on ACTH and cortisone, discuss the immunological effects of the adrenal steroids and mention the work of Dougherty, White, and Chase, who have marshalled an impressive array of evidence from animal studies to support the hypothesis that certain adrenal steroids lead to an increase in the circulating antibodies and that this effect is brought about through involution of lymphoid tissue and a release of antibodies contained within the cells. At the present the bulk of evidence fails to support a significant effect of adrenal steroids on antibody formation in man. Inhibition of the local reaction to intradermal injection of tuberculin in hyperimmune guinea pigs has been demonstrated after ACTH and cortisone administration, and both of these medications have prevented anaphylactic reaction in rats following the parenteral administration of egg white. These investigators also state that it is becoming clear that adrenal hormones are capable of inhibiting at least delayed reactions of the tuberculin type when adequate doses are administered for a sufficient period

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of time. It appears possible that the adrenal steroids alter the allergic reaction of tissues that follows the union of antigen and antibody, probably by inhibiting the formation of histamine and accelerating its breakdown. It also appears that ACTH and cortisone may disassociate the harmful effects of hypersensitivity from the beneficial reactions of immunity.

The cytological response produced by the administration of ACTH is one of lymphopenia, eosinopenia, and an increase in the number of circulating polymorphonuclear neutrophils. Its administration ordinarily results in an increase in the reticulocyte count and an increase in the erythrocyte count in the presence of anemia. Normal and elevated erythrocyte counts are usually unaffected by ACTH. After the discontinuance of hormone therapy there is usually a rise of eosinophils within 3 days, characterized by a rebound over and above the initial pretreatment control level. There does not appear to be any effect on the platelets.

At the present time the only case that could be found in the literature of the use of cortisone or ACTH in the treatment of agranulocytosis was presented by Caldwell, Adams, Anderson, and Dick[2]. They successfully treated a patient with agranulocytosis due to the prolonged use of sulfadiazine, sulfamerazine, and sulfamethazine in combination, by using cortisone. This case did not appear to be as critical as the one which will be discussed; however, the response was essentially the same and very dramatic.

Case Report. The patient was a healthy, robust, 36-year old, deep sea diver who, on November 12, 1950, developed caisson disease. He was 170 feet below the surface of the water for 45 minutes and had only 5 minutes' decompression time while returning from this depth. He rapidly developed nausea, vomiting, intense abdominal pain, and weakness of the legs which progressed to complete paraplegia with anesthesia up to the nipple level of the chest. A decompression chamber was not available and he was treated with oxygen and other conservative measures at another hospital. He had a "cord bladder", with incontinence of urine necessitating an indwelling catheter, and developed cystitis which was treated for several days with penicillin. He was transferred to this hospital on November 22, 1950, 10 days after the accident.

At the time of his admission he still had paraplegia, weakness of abdominal and back muscles, and anesthesia up to the nipple level. He also had a fine, erythematous rash over most of his body which had come on during penicillin therapy and was considered to be due to a sensitivity reaction to penicillin. It subsided rapidly with administration of pyribenzamine. Five days after admission he again developed cystitis and was placed on sulfadiazine, 1.0 gm. 3 times daily. His only other treatment at that time was physiotherapy and B-complex vitamins. On his 12th hospital day the patient began complaining of cough, left chest pain, chills, and fever. His temperature was 103.6° and a roentgenogram of the chest showed a small patch of pneumonic infiltration in the lower lobe of the left lung. He had been maintained on the above dose of sulfadiazine to control cystitis. Because of his previous reaction to penicillin, the dose of sulfadiazine was increased to 1.0 gm. every 4 hours, and the penicillin was withheld. He was worse the following day so was placed also on aureomycin, 500 mg. every 6 hours. His symptoms and fever gradually subsided over a period of 7 days and his medications were discontinued. At that time, December 12, 1950, a routine white blood count, which previously had been either elevated or within normal limits ranging from 7,200 to 13,200, was found to be 2,900 per cc. mm. with neutrophils 39%, lymphocytes 60% and monocytes 1%. During the next 6 days his white count steadily fell to a low of 450 cells, all of which were lymphocytes. At this time the patient was extremely ill. He had chills and fever to 105 degrees, with profuse diaphoresis. His respirations were rapid and shallow, he had moderate cyanosis of the lips and nail beds, and developed a gallop rhythm of his heart. His pulse ranged from 90 to 103 and his death appeared imminent. A sternal marrow stud, was done and showed an almost complete arrest of maturation of the myeloid cells occurring at the progranulocyte stage.

On December 19, 1950, 25 mg. of ACTH were given and continued every 6 hours for 3 days. The dose was then cut to 15 mg. every 6 hours, continued for 2 days, and then cut further to 10 mg. every 6 hours and continued for another 2 days. The patient received a total dose of 500 mg. over a period of 7 days. The response was rapid and very dramatic as the accompanying graph of total white blood counts demonstrates. Within 24 hours the patient stated he felt much better. The gallop rhythm, dyspnea, and cyanosis had largely subsided. After 72 hours the temperature had returned to normal and the patient was asymptomatic except for his paraplegia.

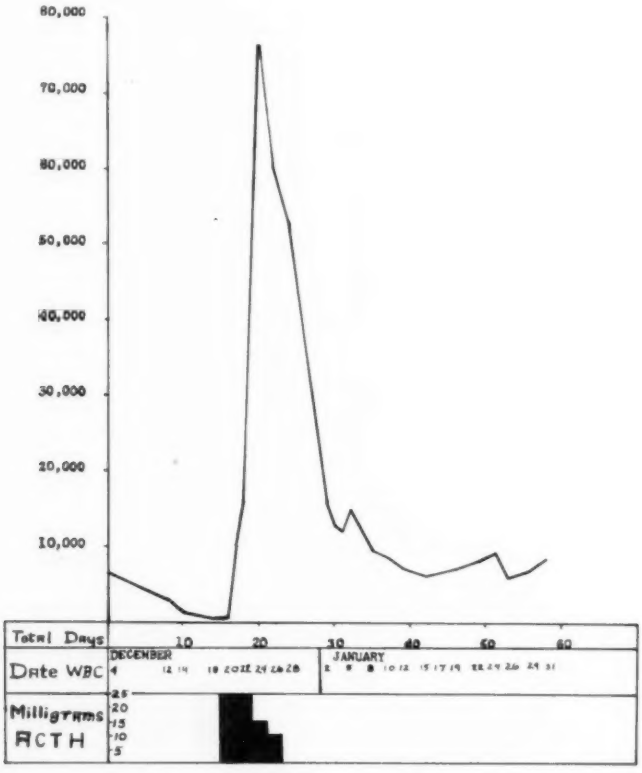

FIG. 1.—Graph showing total white blood cell count before and after treatment with ACTH in a patient with agranulocytosis due to sulfadiazine.

A bone marrow study done 2 days after ACTH therapy was begun showed marked change. Although the cellular content of the marrow was still much dominated by myeloblasts and progranulocytes, there was evidence of further granulocytic differentiation, and a few myelocytes, metamyelocytes, and even mature polymorphonuclear cells were observed. The nuclear differentiation had far outstripped cytoplasmic and granule differentiation; not infrequently metamyelocytes were observed with immature blue cytoplasm and azurophil granules. A third marrow examination done 10 days after ACTH therapy was begun showed marked granulopoietic activity without evidence of maturation defect.

During the time that the white count was markedly elevated peripheral blood smears showed a very bizarre leukocyte picture. Several progranulocytes, myelocytes, and metamyelocytes were observed, as well as more mature forms. Many mature and near-mature neutrophils exhibited basophilic granulations suggesting either toxic granulation or failure of cytoplasmic granular differentiation to keep pace with nuclear differentiation. Subsequent smears showed a gradual decrease in the number of immature forms and a progressive return to a more nearly normal peripheral blood smear. On January 8, 1951, the white blood count was 9,500 with 73% polymorphonuclear cells, 24% lymphocytes, and 3% monocytes. At the date of writing, 50 days after the onset of agranulocytosis and 31 days after cessation of treatment with ACTH, the peripheral blood has continued to remain within normal limits as to total cell count, differential count, and cell morphology, except for a short period of rise in the eosinophil count when the patient developed sensitivity to tincture of benzoin applied to a bed sore. He had a rash at that time which rapidly subsided along with the eosinophil count when the medication was discontinued.

Sensitivity tests to sulfadiazine were contemplated in order that the etiology of the agranulocytosis and its response to ACTH could be positively established. However, they were deemed inadvisable because of the patient's condition.

Summary. 1. Present recommended treatment for agranulocytosis is unsatisfactory in many instances.

2. The immunologic and antiallergenic properties of ACTH and cortisone are briefly discussed along with the cytologic response to their administration.

3. A case of severe agranulocytosis, treated with ACTH with rapid and apparently complete recovery, is presented.

The author expresses his appreciation to Dr. Q. B. DeMarsh, hospital consultant in hematology, for this help and advice, and to Dr. Stanley K. Davis of the Pathology department of the hospital for his excellent reports of examination of the numerous sternal marrow and peripheral blood smears.

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THE EFFECT OF ANTIBIOTICS (PENICILLIN, AUREOMYCIN, AND TERRAMYCIN) ON THE FATALITY RATE AND INCIDENCE OF COMPLICATIONS IN PNEUMOCOCCIC PNEUMONIA. A COMPARISON WITH OTHER METHODS OF THERAPY

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The dramatic drop in the death rate from pneumonia following the introduction of the sulfonamides, and later of penicillin, is now common knowledge. As a result of these spectacular changes, the impression has become prevalent that we have now reached an "irreducible minimum" of deaths from pneumonia in this country, that the conquest of pneumonia is therefore complete, and that the treatment of patients with pneumonia no longer presents any problem.

Before accepting these conclusions, it seemed important to us to find out the reasons for the deaths which still occur among patients with pneumonia while they are receiving approved antibiotic therapy and whether anything can be done to prevent these deaths. Since the pneumococci cause the great majority of all bacterial pneumonias and since the bacterial pneumonias are responsible for nearly all the deaths which occur as a result of pneumonia, we have analyzed our data on patients with pneumococcic pneumonia. Records were available for all of the adult patients with this disease who were treated by us at the Gallinger Municipal Hospital from September 1, 1938, through May 31, 1950. Only those cases in which a pneumococcus was typed from the sputum, blood, and/or other body fluid or exudate have been included. Many of these cases have been reported previously in connection with special studies on pneumonia[1,3-11].

Analysis of Patients. All patients treated with sulfonamides have been grouped together. They received either sulfapyridine, sulfathiazole, sulfadiazine, sulfamerazine, sulfamethazine, gantrisin, or combinations of these drugs. The few patients who received specific anti-pneumococcic serum in addition to sulfonamides have been placed in the sulfonamides group. Patients treated with penicillin, aureomycin, or terramycin have been placed in the antibiotics group. A small number of patients who received both penicillin and sulfonamides have been classified as receiving antibiotics. There were 1,274 patients in the sulfonamides group and 920 patients in the antibiotics group.

The Relationship of Age to Death from Pneumonia. In Table 1 and Fig. 1, the patients have been arranged according to their ages and have been compared with 1,087 patients who received no specific treatment and 889 patients who were given specific anti-pneumococcic serum. The two latter groups were made up of cases reported

TABLE 1.—CASE FATALITY RATES IN PNEUMOCOCCIC PNEUMONIA ACCORDING TO AGE OF PATIENTS AND METHOD OF TREATMENT

	No Specific Treatment			*Treated with Specific Serum*			*Treated with Sulfonamides*			*Treated with Penicillin, Aureomycin or Terramycin*		
Age Group	*No.*	*Died*	*% Died*	*No.*	*Died*	*% Died*	*No.*	*Died*	*% Died*	*No.*	*Died*	*% Died*
10 to 19	115	3	3	121	2	2	116	3	3	64	1	2
20 to 29	172	20	11	170	7	4	279	9	3	162	2	1
30 to 39	216	45	21	247	30	12	357	34	10	251	8	3
40 to 49	222	71	32	172	35	20	236	33	14	207	7	3
50 to 59	175	83	47	85	31	36	141	31	22	107	9	8
60 to 69	101	50	50	72	30	42	90	26	29	72	11	15
70 and over	86	59	68	22	15	68	55	21	38	57	9	16
All cases	1087	331	30.5	889	150	16.9	1274	157	12.3	920	47	5.1

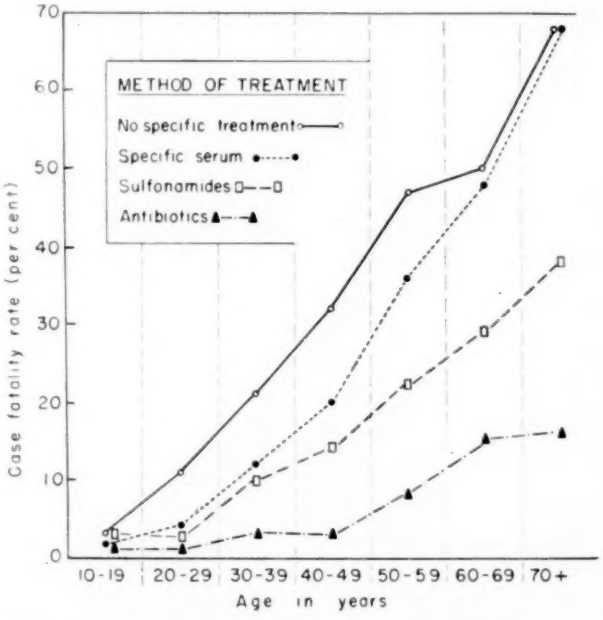

FIG. 1.—Case fatality rates in patients with pneumococcic pneumonia in relation to age.

from the Boston City Hospital by Finland and his associates[2,13-15] and from the Cincinnati General Hospital by Ruegsegger and his coworkers[17], and of patients treated by one of us (H. F. D.) at the Gallinger Municipal Hospital prior to 1938. In contrast to the over-all case fatality rate of 30.5% for patients who received no specific treatment, the fatality rate for patients treated with specific serum was 16.9%, and for those treated with sulfonamides, 12.3%. The fatality rate following treatment with the antibiotics (5.1%) was considerably lower than that achieved by any of the previous methods of therapy. The effect of age upon these rates is shown particularly well in Fig. 1. In patients treated symptomatically the fatality rate rose pro-

gressively with age. Specific serum produced a pronounced reduction in the age groups from 20 through 59, but apparently had no effect in patients over the age of 69. Among the patients who were treated with sulfonamides there were fewer deaths at all ages from 30 years on than in the patients who received serum, although the fatality rates for patients over the age of 49 years were still high in the sulfonamides group. The antibiotics were responsible for a further lowering of the fatality rates from the age of 30 years on, although it should be noted that even in patients over the age of 59 years the fatality rate was still 15%.

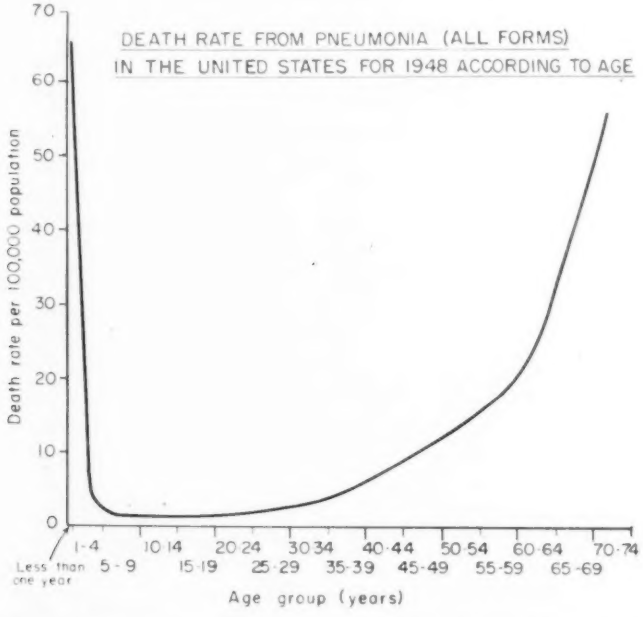

FIG. 2.—Death rates from pneumonia (all forms) in the United States for the year 1948 according to age.

It is unfortunate that we do not have sufficient data on children and infants to determine the effect of present-day treatment on recovery in those age groups. Some idea of the relationship of age to death from pneumonia in this period of life can be obtained, however, from Fig. 2, which portrays the death rate per hundred thousand of population in the United States for the year 1948[16]. By that year, it may be assumed, penicillin treatment was available to everyone, so that these results are probably typical of those which can be obtained when present-day therapeutic measures are employed under the current methods of medical care. From Fig. 2 it is evident that the highest mortality rates occur in infants under 1 year of age and in persons over 64 years of age. The steady rise in the mortality rate from ages 35 to 65 years is still a challenge to our therapeutic skills.

RELATION OF BACTEREMIA TO PROGNOSIS. Among the factors which make for a poor prognosis, bacteremia has always been considered one of the most important. An admission blood culture

was taken on all our patients and in some cases, where the response to therapy was not satisfactory, additional blood cultures were obtained. This information is shown in Fig. 3. Among the 96 patients with positive blood cultures who were treated with antibiotics in our series, 13 (13%) died, whereas among 972 patients with negative blood cultures, 37 (4%) died. The corresponding figures for patients treated with sulfonamides were: among 159 patients with bacteremia, 46 (29%) died; among 957 patients without bacteremia, 100 (10%) died. The difference between the fatality rates in sulfonamide- and antibiotic-treated patients, in both the bacteremic and non-bacteremic groups, is highly significant by the chi square test. The relation of bacteremia and age to the results of treatment with sulfonamides and with antibiotics is shown in Fig. 3. All of the differences shown for the sulfonamides group were significant by the chi square test. Among the patients under the age of 50 years who were treated with antibiotics the difference between the 12% and the 2% case fatality rates in patients with and without bacteremia, respectively, was statistically significant. Among the patients over the age of 49 years the difference between the fatality rates of 17% for those with bacteremia and 10% for those whose blood cultures were negative was not statistically significant.

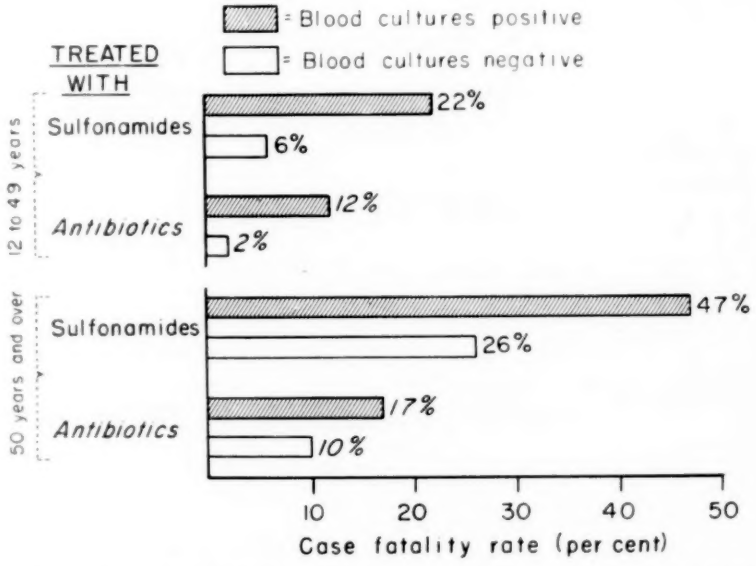

FIG. 3.—Case fatality rates in patients with pneumococcic pneumonia in relation to bacteremia.

It seems likely that in patients treated with sulfonamides both age and the presence of bacteremia were important in relation to the outcome of the pneumonia. In patients treated with antibiotics the presence or absence of bacteremia was an important prognostic sign in patients under the age of 50 years. In patients over the age of 49 years who received antibiotic therapy, other factors apparently played a greater part in determining the prognosis than the presence of detectable

numbers of pneumococci in the blood stream. One of these factors was undoubtedly the presence of the complicating diseases which frequently occurred in the older persons, and another may have been the physiological effect of age itself upon the defense mechanism of the patient.

Relation of Early Treatment to Prognosis. If a therapeutic agent is effective in an infectious disease, its value is usually directly proportional to the promptness with which treatment is begun. We have divided our patients into those whose treatment was started during the first 4 days of the disease and those whose treament was begun on the 5th day or later. The patients above or below 50 years of age were then analyzed separately. The results are shown in Fig. 4.

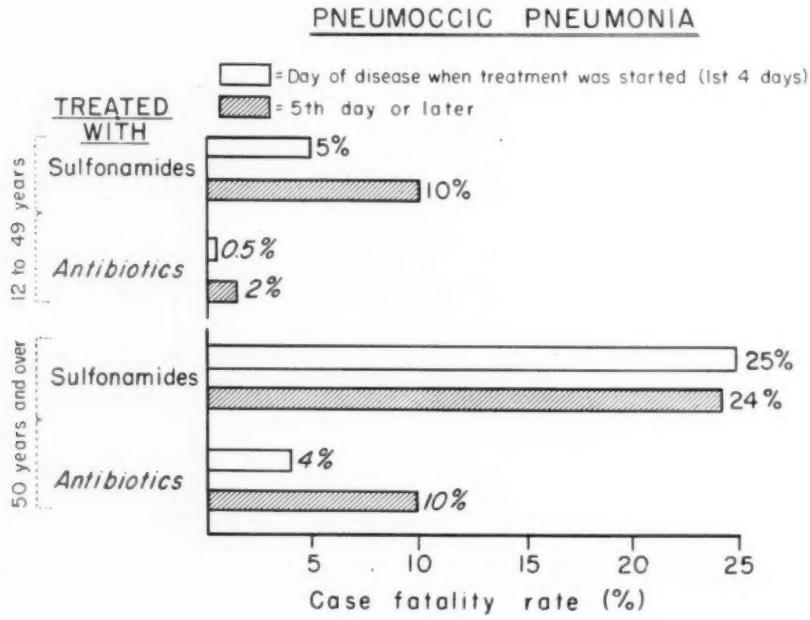

Fig. 4.—Case fatality rates in patients with pneumococcic pneumonia in relation to the time treatment was started.

In the group of patients under 50 years of age who were first treated with sulfonamides during the first 4 days of the disease, 5% of the patients died, as compared to 10% of the patients whose treatment was started after the 4th day. This difference is statistically significant. Among patients over the age of 49 years who were treated with sulfonamides, the day of disease when treatment was started appeared to have no effect upon the prognosis. Among the patients who were treated with antibiotics the fatality rates were lower for patients of all ages when therapy had been started before the 5th day of the pneumonia than when therapy was begun later than this. The differences were not statistically significant, however, due to an insufficient number of cases.

It would seem, therefore, that the promptness with which treatment was initiated made for a better prognosis if the therapeutic agent was sufficiently

effective, as in the younger patients treated with sulfonamides and patients of all ages treated with antibiotics. On the other hand, where the course of the disease was unfavorable as in patients in the 6th and later decades of life, sulfonamides were apparently not sufficiently effective to bring about the recovery of a significant proportion of the patients if treatment was started late.

Relation of Type of Pneumococcus to Prognosis. We have analyzed our series of antibiotic-treated patients to determine the relationship of the type of the infecting pneumococcus to the outcome of the disease. When the factor of age was excluded, there was a slightly higher fatality rate for patients with Type III pneumococcic pneumonia than for patients with pneumonias caused by the other commonly encountered types. This difference between types was not so pronounced, however, as in patients who were treated with sulfonamides or serum, or in patients who were symptomatically treated. The other factors previously mentioned, such as age of the patient, presence of bacteremia, and promptness of treatment, were relatively more important.

Complications of Pneumonia. The complications which occurred in the 1,250 patients treated with sulfonamides and in the 750 patients treated with penicillin, aureomycin, or terramycin have been tabulated and are shown in Table 2. Only those complications are included which were observed to develop after treatment with sulfonamides or antibiotics was started in our hospital. It will be seen that the percentage of patients with delayed reso-

TABLE 2.—INCIDENCE OF COMPLICATIONS OF 2,000 CASES OF PNEUMOCOCCIC PNEUMONIA TREATED WITH SULFONAMIDES OR ANTIBIOTICS

	Incidence among:			
	1,250 Patients Treated with Sulfonamides		*750 Patients Treated with Antibiotics*	
Complication	*Number of Cases*	*Incidence (%)*	*Number of Cases*	*Incidence (%)*
Delayed resolution	32	2.6	29	3.8
Pleural effusion	20	1.6	8	1.1
Empyema	24	1.9	5	0.7
Relapse	22	1.8	9	1.2
Lung abscess	10	0.8	1	0.1
Meningitis	8	0.6	3	0.4
Endocarditis	7	0.6	1	0.1
Pericarditis	5	0.4	1	0.1
Otitis media	5	0.4	2	0.3
Arthritis and/or bursitis	4	0.1	1	0.1
Subcutaneous abscess			1	0.1
Total bacterial complications (excluding delayed resolution and pleural effusion)	85	6.8	24	3.2

lution and uninfected pleural effusion was essentially the same in the sulfonamide-treated and in the antibiotic-treated groups. The bacterial complications, however, were less than half as frequent among the antibiotic-treated patients (3.2%) as among the sulfonamide-treated patients (6.8%).

Analysis of Individual Deaths. If penicillin, aureomycin, and terramycin are so effective in the great majority of cases of pneumococcic pneumonia, why, then, do any patients die? Some of the reasons have already been given. Patients who die are usually in the older age groups, often have bacteremia, and are often treated late in the disease. Further analysis of the reasons for death cannot be done profitably on a quantitative basis; each case must be examined individually. When this was done for the patients in our series, it was evident that the patients under 50 years of age who succumbed to pneumococcic pneumonia were either treated late in the disease or had some complicating condition present. Complicating conditions which we considered significant were: congestive heart failure or auricular fibrillation, cerebral hemorrhage, bronchiectasis, delirium tremens, diabetic coma, uremia, and cirrhosis of the liver. The same causes operated in patients who were 50 years of age or over and who died, except that an occasional patient died from a complication of the disease itself, such as empyema, meningitis, endocarditis, pericarditis, or, in one case, perforation of a distended transverse colon.

Discussion. Despite the dramatic fall in the case fatality rate in pneumococcic pneumonia during recent years, many patients still die from the disease. Our studies confirm the fact that in every way the antibiotics are superior to the sulfonamides in the treatment of this disease, but they also show that we can do better than we are doing now. These data present several challenges to the medical and public health professions:

1) Many patients are still not treated early enough. Education of the public to report promptly any symptoms which are suspicious of pneumonia has been nearly forgotten as a result of the all-too-prevalent impression that the "wonder drugs" can take care of anything. Such education is obviously still needed.

2) Persons with heart disease, nephritis, bronchiectasis, tuberculosis, cirrhosis of the liver, diabetes mellitus, or similar chronic diseases must be watched carefully for the onset of pneumonia and treated vigorously with antibiotics at the onset of the disease.

3) Alcoholics compose the largest single group of persons who die among adults under the age of 50. Now that our attitude toward the alcoholic is becoming more enlightened and we are seeking methods which will turn these people into useful and productive citizens, we must be more than ever on guard that pneumonia does not carry them off before we have a chance to get to the roots of the alcoholism and eradicate it.

4) Older persons still represent an important problem in the treatment of pneumococcic pneumonia. While only 26% of our cases of pneumonia were in persons over 49 years of age, 62% of our deaths fell in these age groups. Older persons should be under medical supervision and should be promptly treated with antibiotics when there is reasonable evidence that pneumonia is present. The data presented in Figs. 1 and 3 demonstrate the effectiveness of antibiotics in these age groups. Physicians caring for patients in the older age groups may do well to adopt the pediatricians' attitude toward the prompt use of antibiotics when a bac-

terial infection of the respiratory tract is suspected. This is important because pneumonia in the aged may be accompanied by little or no fever and may exhibit none of the cardinal signs of pneumonia. Consideration should be given to immunizing persons above the age of 60 or 70 years with pneumococcal polysaccharides. This has been shown by Kaufman[16] to be a practical and effective procedure.

Summary. 1) In a series of 2,194 patients over 10 years of age with pneumococcic pneumonia, 1,274 patients were treated with sulfonamides and 920, with penicillin, aureomycin, or terramycin.

2) The case fatality rate for all patients treated with antibiotics was 5.1%, compared to 12.3% for sulfonamides. The case fatality rate for patients over the age of 59 years who were treated with antibiotics was 15%.

3) The relationship of bacteremia, promptness of treatment, type of infecting pneumococcus, and complicating diseases has been analyzed and the significance of these factors discussed.

4) Bacterial complications of pneumococcic pneumonia appeared in 3.2% of patients under treatment with antibiotics as compared to 6.8% of patients who were treated with sulfonamides.

5) It is concluded that early diagnosis and treatment of patients with pneumococcic pneumonia and particular attention to persons in the older age groups and to patients with chronic diseases can result in a further decrease in the number of deaths from from this disease.

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STUDIES ON ANTIBIOTIC SYNERGISM AND ANTAGONISM: THE INTERFERENCE OF AUREOMYCIN, CHLORAMPHENICOL AND TERRAMYCIN WITH THE ACTION OF STREPTOMYCIN*

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The availability of a number of satisfactory antimicrobial agents makes the use of combinations of these agents tempting to the clinician. The increasing frequency of drug-resistant microorganisms often makes such use necessary. Although the indiscriminate administration of antibiotic mixtures should not be condoned, it is virtually certain to increase in the every-day practice of medicine. Following the introduction of each new drug, resistant bacteria are soon discovered and the physician feels forced to resort to combinations of drugs in the hope of obtaining additive or synergistic effects.

The information available on the effects of combinations of antibacterial agents is not adequate to provide broad rules for the guidance of practicing physicians. On the basis of precise laboratory examinations[9,12] drug combinations may be selected for individual patients where single drugs have failed. In addition to this individual service, the laboratory might well be expected to provide more general guiding lines for rational combined antimicrobial therapy and to lay the foundation for an understanding of the principles involved.

Because of this manifest need, studies have been undertaken to define some of the effects of combined antimicrobial therapy. Based on *in vitro* and *in vivo* observations, certain drug combinations have been found to exhibit markedly increased effects over the single drugs. Combinations of penicillin with streptomycin or with bacitracin were clearly synergistic in their action against certain bacteria[10] and spirochetes[1] and clinical observation has substantiated this experimental evidence[7,14].

Conversely, it has been shown experimentally that certain combinations of antibacterial drugs result in antagonism and diminished effect. Previous publications from this laboratory have dealt with the ability of chloramphenicol, aureomycin, and terramycin to interfere with the bactericidal and therapeutic effects of penicillin[3,11,15]. Marked antagonism was observed

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in these combinations *in vitro* and in experimental infections of mice with both gram positive (*Streptococcus*) and gram negative (*Klebsiella*) organisms. The possible mechanism of interference was attributed to the fact that penicillin was most active against rapidly multiplying bacteria and that the "interfering drug" slowed multiplication and thus blocked optimal penicillin action[11].

This report deals with the interference of aureomycin, chloramphenicol, or terramycin with the action of streptomycin *in vitro* and in experimental infections of mice.

Materials and Methods. BACTERIA. The organisms employed were the same as in previous work[3,11], a beta hemolytic *Streptococcus pyogenes* group A, type 3, strain C 203, and a *Klebsiella pneumoniae* strain A-D. The organisms were kept at peak virulence by means of frequent and rapid animal passage. The LD_{50} for mice by intraperitoneal injection of the *Streptococcus* was 1 to 10 organisms, and of the Klebsiella, 20 to 200.

BACTERIOLOGICAL MEDIA AND TECHNIQUES. These were identical with those employed in previous studies[3,11,15].

ANTIBIOTICS. Commercial streptomycin sulfate was dissolved in sterile saline solution to make a stock solution of 50 mg. per cc. which was kept at 4° C. Solutions of the desired strength were prepared from this stock prior to each test. Aureomycin hydrochloride (Lot No. 7-6116)*, terramycin hydrochloride (Lot WBW 507019)†, and crystalline chloramphenicol (Lot 134006)** were dissolved in buffered saline solution (pH 7.2) to make a concentration of 1.0 or 2.0 mg. per cc. The solutions were then sterilized by Seitz filtration. The aureomycin solution was quickly frozen and stored at −20° C.; the others were kept at 4° C. for the duration of the study.

EXPERIMENTAL INFECTION AND THERAPY. White Swiss mice weighing approximately 20 gm., from a heterozygous stock, were used in all experiments in groups of 20 animals. Cultures of bacteria were grown in 5% sheep blood broth at 37° C. for 18 hours. The animals were infected by the intraperitoneal injection of 0.2 cc. of a 10^{-5} dilution of culture in broth, containing 10 to 100 LD_{50}. Untreated animals usually died within 2 to 4 days after infection. Drugs were administered intraperitoneally in a volume of 0.2 cc. each. Previous experience[11] had indicated that results were similar, whether the drugs were injected into the same or into different sites. The time and dosage of treatment varied in different experiments as indicated below. The animals were observed for 10 days and deaths were recorded. Calculations of LD_{50} and CD_{50} were according to the method of Reed and Muench[13]. Differences in death rates of groups of animals were considered significant only if they exceeded 30%. Cause of death was ascertained in occasional mice by recovery, in pure culture, of the infecting organism from heart blood.

Results. 1. THE INTERFERENCE OF AUREOMYCIN, CHLORAMPHENICOL, AND TERRAMYCIN WITH THE ACTION OF STREPTOMYCIN IN VITRO. Previous communications from this laboratory have dealt with the ability of the 3 "newer" antibiotics to interfere with the bactericidal action of penicillin *in vitro*, and have defined the relative magnitude of this antagonism. Fig. 1 illustrates that these 3 drugs are likewise capable of interfering *in vitro* with the bactericidal effect of streptomycin against *K. pneumoniae*. In comparing the antagonistic effects of 1 mcgm. per cc. of each of the drugs, the graphs indicate that chloramphenicol interferes more markedly than the other 2 agents. This *in vitro* phenomenon is only transient. Antagonism is most marked during the first 12 hours of incubation. Subsequently the tubes containing the 2 drugs are more likely to become sterile than those containing streptomycin alone, where resistant organisms grow out between 24 and 48 hours of incubation. As in the case of antagonism to penicillin, the 3 drugs appear to interfere principally

* Kindly supplied by Dr. S. H. Hardy, Lederle Laboratories, Pearl River, N. Y.
† Kindly supplied by Dr. H. H. Anderson, University of California, School of Medicine.
** Kindly supplied by Dr. G. Rieveschl, Parke Davis & Company, Detroit, Michigan.

with the early bactericidal action of streptomycin.

Limited experience with a range of concentrations of the 3 "interfering" drugs indicates that the degree of interference is a function of their biologic activity. Interference is most pronounced with concentrations exhibiting marked bacteriostasis. Higher concentrations which are bactericidal by themselves show less evident antagonism to streptomycin action.

organisms. Accordingly, twice-washed *K. pneumoniae* were suspended in Ringer's solution and exposed to penicillin or streptomycin alone or combined with chloramphenicol (Fig. 2). Under these conditions no multiplication of organisms took place in the drug-free control tubes. Streptomycin was rapidly bactericidal in the same concentrations that were effective against multiplying bacteria, whereas penicillin was active only in concentrations 100

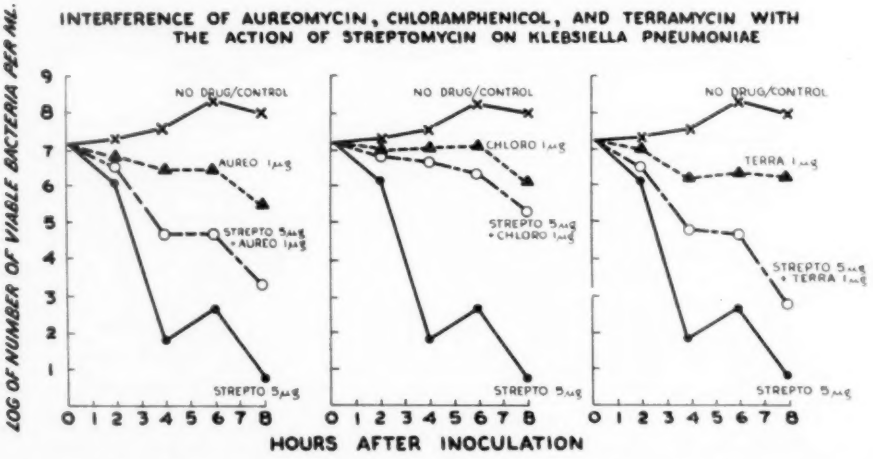
INTERFERENCE OF AUREOMYCIN, CHLORAMPHENICOL, AND TERRAMYCIN WITH THE ACTION OF STREPTOMYCIN ON KLEBSIELLA PNEUMONIAE
LOG OF NUMBER OF VIABLE BACTERIA PER ML.
NO DRUG/CONTROL
AUREO 1 µg
STREPTO 5 µg + AUREO 1 µg
STREPTO 5 µg
CHLORO 1 µg
STREPTO 5 µg + CHLORO 1 µg
TERRA 1 µg
STREPTO 5 µg + TERRA 1 µg
HOURS AFTER INOCULATION

FIG. 1.—The ability of 1 microgram (mcgm.) of aureomycin, chloramphenicol, or terramycin to interfere with the early bactericidal effect of 5 mcgm. of streptomycin in *Klebsiella pneumoniae*.

The similarity between the results with streptomycin and those previously encountered in the antagonism of these drugs to penicillin raises the question of a similar mechanism being involved. While penicillin is most effective against rapidly multiplying organisms, streptomycin is bactericidal for both multiplying and non-multiplying bacteria[5,6]. If the hypothesis is correct that the antibiotic antagonism described here depends upon a reduction in rate of bacterial multiplication by the "interfering" drug, antagonism should not be demonstrable when drug combinations act on non-multiplying

times greater than those affecting multiplying *K. pneumoniae*. Chloramphenicol did not interfere with the action of either penicillin or streptomycin in Ringer's solution. Apparently chloramphenicol does not antagonize these antibiotics under conditions which do not permit multiplication of micro-organisms.

The same problem was approached from another direction by comparing the effect of an "interfering" drug on a susceptible micro-organism and on a resistant variant. A terramycin-resistant culture of *K. pneumoniae* was used to test the hypothesis that antagonism

is related to a reduced rate of bacterial multiplication in the presence of the interfering drug. There was no interference with the action of streptomycin on this culture in broth by a concentration of terramycin which was not bacteriostatic (0.5 mcgm./cc.), whereas a greater concentration (100 mcgm./cc.) was bacteriostatic and showed transient interference. With a terramycin-sensitive culture of the same organism, on the other hand, 0.5 mcgm./cc. of terramycin exhibited maximal interference with streptomycin, whereas 100 mcgm./cc. was highly active alone but not antagonistic. Thus there is further evidence that antagonism is not chiefly a function of the concentration of the interfering drug but rather of its biologic activity against specific micro-organisms.

2. Interference of Antibiotics with the Therapeutic Effect of Streptomycin in Experimental Infections of Mice. Antagonism between chloramphenicol and streptomycin was readily demonstrated in the experiment summarized in Table 1. When single injections of drug were given 1 hour after infection, streptomycin alone cured 30 to 50% more animals than did streptomycin plus chloramphenicol. Small amounts of chloramphenicol interfered with low, but not with high, doses of streptomycin. The latter were more effectively antagonized by the larger amounts of the interfering drug.

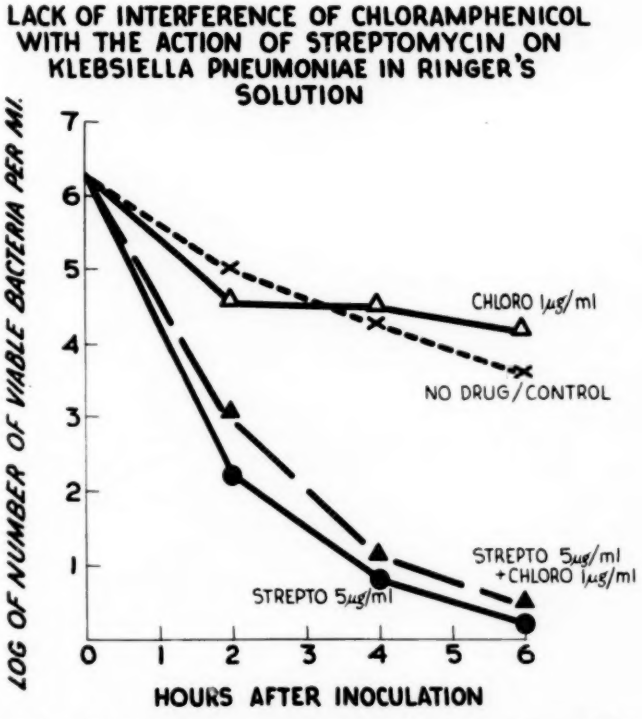

Fig. 2.—In Ringer's solution 5 mcgm. of streptomycin is rapidly bactericidal for washed suspensions of *K. pneumoniae*, whereas 1 mcgm. of chloramphenicol has virtually no effect. The addition of chloramphenicol to streptomycin does not diminish the early bactericidal rate.

A more complete picture of the relative degree of antagonism exhibited by various doses of chloramphenicol in a streptococcal infection of mice is given in Fig. 3. Streptomycin doses of intermediate therapeutic efficacy (for example, 200 mcgm./mouse) were effectively antagonized by a wide range of chloramphenicol concentrations. The low solubility of chloramphenicol limited satisfactory determinations at the upper end of the curve.

TABLE 1.—INTERFERENCE OF CHLORAMPHENICOL WITH THE THERAPEUTIC EFFECT OF STREPTOMYCIN IN A STREPTOCOCCAL INFECTION OF MICE

Chloramphenicol mcgm./mouse	*Rate of survival in infected mice receiving Streptomycin mcgm./mouse*			
	0	*200*	*300*	*500*
None	0–7.5*	60†	80	85
50	12.5	7.5	50	75
200	10	15	25	Not done
400	7.5	15	50	45

* Untreated controls.
† Per cent survival, based on groups of 20 to 40 animals.
A single dose of drug was administered intraperitoneally 1 hour after the intraperitoneal injection of 100 LD_{50} of *Streptococcus* C 203.

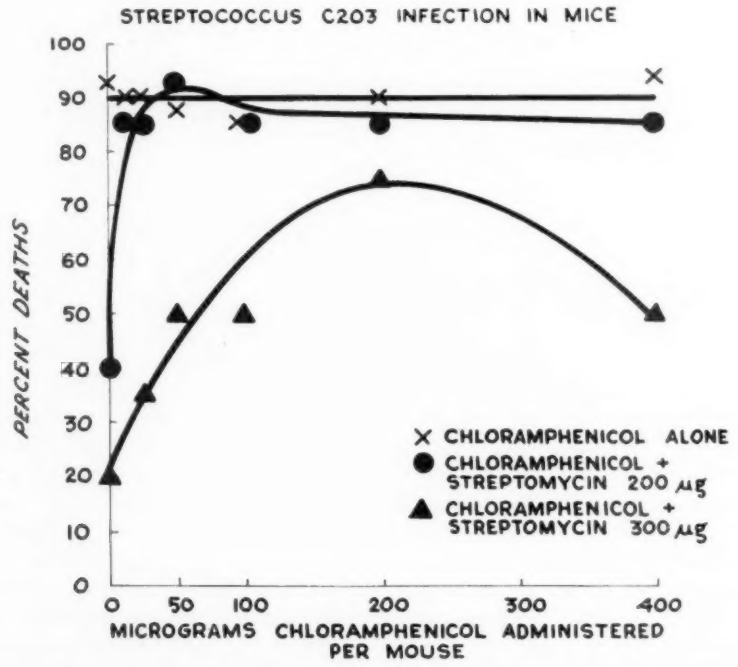

FIG. 3.—The effect of adding increasing amounts of chloramphenicol to 200 or 300 mcgm. of streptomycin injected into mice intraperitoneally 1 hour after intraperitoneal infection with 100 LD_{50} of *Streptococcus* C 203.

In multiple dose schedules, antagonism was likewise definite. With the administration of 100 mcgm. of streptomycin and 10 or 50 mcgm. of chloramphenicol at 1, 5, and 9 hours after infection with *Streptococcus* C 203, the death rate of groups treated with both drugs exceeded by 30% that of the group treated with streptomycin alone (Fig. 4).

A dose of chloramphenicol capable of interfering with a therapeutic dose of either penicillin or streptomycin in a streptococcal infection of mice failed to have any effect against penicillin and streptomycin employed together (Table 2). This parallels to some extent the previous finding[4] that streptomycin can overcome the chloramphenicol-penicillin antagonism. It has

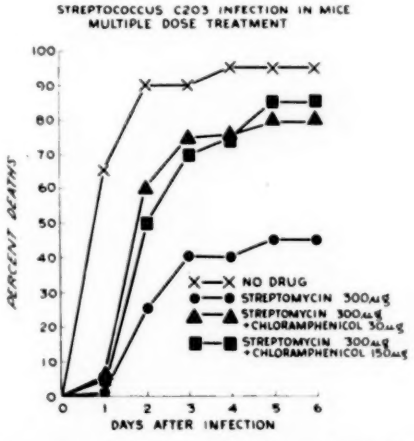

FIG. 4.—Streptomycin (100 mcgm.) alone, or with chloramphenicol (10 or 50 mcgm., respectively) was injected intraperitoneally at 1, 5, and 9 hours, after intraperitoneal injection of 100 LD_{50} of *Streptococcus* C 203.

TABLE 2.—THE EFFECT OF SIMULTANEOUS ADMINISTRATION OF CHLORAMPHENICOL, PENICILLIN, AND STREPTOMYCIN IN A STREPTOCOCCAL INFECTION OF MICE

Penicillin subcutaneously mcgm./mouse	*Streptomycin intraperitoneally mcgm./mouse*	*Chloramphenicol intraperitoneally mcgm./mouse*	*% Deaths**	*Interference*
100	0	0	10	
0	500	0	25	
0	0	200	95	
100	500	0	0	None
0	500	200	70	Definite
100	0	200	70	Definite
100	500	200	10	None
0	0	0	100	

* Based on groups of 20 mice.
The drugs were injected 1 hour after intraperitoneal infection with 100 LD_{50} of *Streptococcus* C 203.

not yet been established to what extent higher chloramphenicol doses might block the combined effect of penicillin and streptomycin.

Significant interference of chloramphenicol with the therapeutic action of streptomycin was also observed in mice infected with *K. pneumoniae*. In a limited number of experiments with this organisms the same broad dose relationships were encountered as those described above for a streptococcal infection.

were of similar design, there was marked antibiotic antagonism in experiment B but none in A. The addition of 2 to 10 mcgm. of aureomycin to 500 mcgm. of streptomycin raised the death rate from 20 to 55% in experiment B but had no significant effect in A. The outstanding differences between experiments A and B are the lower therapeutic effectiveness of aureomycin alone in B, together with a somewhat more active dose of streptomycin. Thus apparently minor

TABLE 3.—THE RELATIONSHIP OF THE ANTIBACTERIAL ACTIVITY OF THE "INTERFERING" DRUG TO THE OCCURRENCE OF ANTIBIOTIC ANTAGONISM

Experiment	*Streptomycin mcgm./mouse*	*% of Survival in Infected Mice Receiving Aureomycin mcgm./mouse*					
		0	*1*	*2*	*5*	*10*	*50*
A	None	5*	10	20	30	80	80
	300	65	75	55	65	80	80
B	None	0	10	20	20	0	30
	500	80	75	45	45	45	90

* % survival based on groups of 20 mice.

A single dose of one or both drugs was administered intraperitoneally one hour after the intraperitoneal injection of 100 LD_{50} of *Streptococcus* C 203.

In vitro studies had indicated that chloramphenicol interfered more markedly with the bactericidal effect of streptomycin than either aureomycin or terramycin (Fig. 1). *In vivo* the pattern was similar. Terramycin and aureomycin both interfered with the therapeutic action of streptomycin in infections of mice with a *Streptococcus* or a *Klebsiella*, but to a lesser extent than chloramphenicol. In single-dose experiments the antagonism was demonstrable when aureomycin or terramycin was administered within 5 to 15 minutes of the streptomycin injection. With multiple dose schedules, however, no significant degree of antagonism could be found. A possible reason for such variable results is suggested by experiments summarized in Table 3. Although the 2 experiments

changes in adjustment of drug dosage or in severity of infection may greatly influence the results when antagonism is not of high magnitude. Antagonism of terramycin to streptomycin *in vivo* was of equally low order.

Discussion. In a recent editorial the *British Medical Journal* discussed antibiotic synergism and antagonism[2] and suggested that it might be "a general principle, to which there may be exceptions, not to combine a bacteriostatic with a bactericidal agent of the penicillin type". It then asked whether this observation will prove that either of the two bacteriostatic drugs (aureomycin and chloramphenicol) interferes with the action of either of the bactericidal drugs (penicillin and streptomycin). This question may now be answered in the affirmative. Work in this

laboratory has clearly demonstrated that the bacteriostatic agents aureomycin, chloramphenicol, and terramycin are capable of interfering with the action of streptomycin in a manner similar to that previously reported for penicillin. The magnitude of antagonism to streptomycin is somewhat less than that to penicillin, particularly in multiple dose experiments in a streptococcal infection of mice.

The mechanism postulated for the interference of bacteriostatic antibiotics with the action of penicillin, namely, a reduction in the rate of bacterial multiplication with diminished susceptibility of the micro-organisms to penicillin, may well apply to their interference with streptomycin. Certain differences, however, must be pointed out. Whereas penicillin exerts its maximal antibacterial effect against actively multiplying organisms, that is not the case with streptomycin. In its action against *K. pneumoniae* streptomycin had quantitatively similar effects on resting, washed cell suspensions and on multiplying cultures. Yet the interfering drugs blocked streptomycin action in broth but not in Ringer's solution. It appears, therefore, that the interfering drugs may influence metabolic steps or pathways associated with multiplication.

Bacteriostasis produced by the interfering drug has been a common denominator of the antagonistic effects observed. The nature of the bacteriostatic agent appears also to be of importance. Unpublished experiments in this laboratory have indicated that small, bacteriostatic concentrations of either penicillin or streptomycin never interfere with the rapid, therapeutic effect of a later, large dose of the same drug. Furthermore, no concentration of streptomycin has been shown to interfere with penicillin action, or vice versa, in the test tube or in experimental infections. In this curious "lineup" of drugs, penicillin, streptomycin, and perhaps bacitracin, are in one group; aureomycin, chloramphenicol, and terramycin, in a second group. Drugs of the second group may all, though not to the same degree, interfere with the action of drugs in the first group. The agents of the first group appear to be synergistic with each other, and to be capable of overcoming the interference by the drugs of the second group.

The interference of aureomycin, chloramphenicol, and terramycin with the action of streptomycin *in vitro* and *in vivo* is a unilateral phenomenon. Such interference may therefore be observed only if the infecting microorganism is susceptible to streptomycin. If the bacterium is resistant to streptomycin to begin with, no interference can be observed. On the contrary, with a resistant organism true synergism, with a marked increase in early bactericidal rate, may be demonstrated between streptomycin, and for example, terramycin. A patient illustrating such a problem and cured by this drug combination has been observed[8].

A drug antagonism which can be demonstrated only under highly selected circumstances in experimental infections is unlikely to be of importance in the treatment of clinical disease. The interference of aureomycin and terramycin with the action of streptomycin is probably in this category. Whether the antagonism of chloramphenicol to streptomycin is of sufficient magnitude to cause concern is a question which must be answered by further experimentation and clinical experience.

Summary. 1. Aureomycin, chloramphenicol, and terramycin can interfere with the action of streptomycin *in vitro* and in experimental infections of mice. The antagonism is more marked with

chloramphenicol than with the other 2 agents. It is a unilateral phenomenon which can be observed only with micro-organisms susceptible to streptomycin action.

2. The interference is associated with the inhibition of multiplication of bacteria by the bacteriostatic antibiotics. Although streptomycin is as rapidly bactericidal for the test strain of *Klebsiella pneumoniae* in Ringer's solution as in broth, antibiotic antagonism of significant magnitude can be demonstrated only in the latter. With a terramycin resistant variant as test organism, terramycin fails to antagonize streptomycin, whereas with the terramycin-sensitive parent culture such interference is readily observed.

3. In infections of mice with *Streptococcus* or *Klebsiella* the antagonism of aureomycin and terramycin to the therapeutic action of streptomycin is not of great magnitude, and its demonstration depends on accurate adjustment of drug dosage to severity of infection. It is therefore not likely to be of importance in clinical therapy.

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AUREOMYCIN IN INFECTIOUS MONONUCLEOSIS: A CONTROL STUDY

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Infectious mononucleosis, formerly regarded as benign and relatively uncommon, has assumed medical importance within the past 2 decades[6]. Diagnosed with increasing frequency, its ability to cause pathology in any organ, its protracted course and stubborn refractoriness to therapy with occasional termination in death, are eradicating the notion that mononucleosis is benign[4,7,13,14].

Infectious mononucleosis exhibits characteristics closely similar to those of other viral diseases and diseases presumably viral in origin. Similarities in clinical picture, progress, and hematology invite therapeutic use of drugs and antibiotics that are regarded as effective against such infections. Excellent results have been reported from use of aureomycin, for example, in many disease states demonstrably or supposedly viral in etiology; these include atypical pneumonia[10,11], psittacosis[15], lymphogranuloma venereum[3], herpes zoster[1], and others[9].

A control study is indicated of the use of aureomycin in the treatment of infectious mononucleosis. Such a study is reported herewith.

Method of Study. Appraisal of the therapeutic value of any drug in infectious mononucleosis requires intimate knowledge of the natural history of the disease. In our 3 years' experience with over 800 cases, conspicuous discrepancies in symptoms and course of the disease render impossible any correlation of the clinical picture, the febrile reaction, the progress, or the hematology. Numerous cases that present a diptheric type of pharyngitis show but little fever, leukocytosis, or marked increase in serum agglutination of sheep's red cells. In sharp contrast, other cases are marked by predominance of fever with little other objective evidence of the disease. The highest positive Paul Bunnell tests and leucocytosis have accompanied prolonged fatigue without pronounced disability. Cases of brief duration and slight disability run concurrently with others that exhibit a markedly protracted course. Unless such variations are recognized and known intimately, interpretation of the effects of any drug may lead to erroneous conclusions.

Most of the cases included in this study are infectious mononucleosis of the so-called pharyngeal glandular type. Restriction to this type is based on the facts that 1) 85% of observed cases fall into this category, and 2) objective findings are less ambiguous and more amenable to clinical evaluation. All these patients were hospitalized and observed for at least 24 hours before therapy was initiated. This period was chosen arbitrarily to fortify the diagnosis and to establish the trend of progress. The latter precaution is

* The cooperation of Dr. Dorothy Naumann is gratefully acknowledged. Aureomycin for this study was kindly furnished by the Lederle Division, American Cyanamid Corporation.

imperative because in this disease symptoms and febrile reactions frequently subside after 24 hours of hospitalization. After this standard interval therapy was begun by administering aureomycin every 6 hours in divided doses of ½ gm.; during administration of aureomycin the only other drugs used were such analgesics as aspirin and codeine. Under these conditions 32 patients were treated actively and 30 patients were maintained as controls.

TABLE 1.—DURATION OF HOSPITALIZATION: CASES OF INFECTIOUS MONONUCLEOSIS TREATED WITH AUREOMYCIN COMPARED WITH UNTREATED CONTROLS

Days Hospitalized	*Treated Cases*		*Untreated Cases*	
	No.	*%*	*No.*	*%*
1–5	8	25	14	46.6
6–10	17	53.1	15	50
11–15	4	12.5	1	3.4
16–20	3	9.4	0	0
	32	100	30	100

Results. In Table 1 the treated cases are compared with the controls. When infectious mononucleosis is treated with aureomycin a dramatic fall in temperature often coincides with the aureomycin therapy and some symptomatic improvement not infrequently occurs. Little change appears, however, in the objective findings or the hematological picture; in fact, analysis of the natural history shows that cases not treated specifically are frequently identical in pattern with cases treated with antibiotics.

The only clear-cut contrasts between treated and untreated cases of mononucleosis appear in the records of those cases in which infectious mononucleosis and pneumonia are observed simultaneously in the same patient. In these latter instances administration of aureomycin has been followed promptly by improvement of both conditions. This immediate thermal and clinical response to aureomycin in our 2 cases that manifested pneumonia in association with infectious mononucleosis deserves attention. No reason appears for the favorable response when pneumonia is present and for failure of response to therapy of uncomplicated mononucleosis.

Sound appraisal of drug therapy and antibiotic therapy in this disease would emerge in observation of the more severe cases. From the present data it cannot be concluded that severe cases of infectious mononucleosis respond favorably to aureomycin therapy.

Of patients with mononucleosis treated with aureomycin, 78.1% were hospitalized 10 days or less; of patients not treated, 96.6% were hospitalized 10 days or less. Three of the treated patients were hospitalized more than 15 days; no untreated patient required such protracted hospitalization.

Effect of Aureomycin on Fusospirochetal Invaders. In our clinic 50 cases in which fusospirochetal infection of the mouth, gums, and pharynx was established bacteriologically have been treated with aureomycin topically and orally. The aureomycin therapy was either in the form of troches (15 mg.) locally, or of capsules orally. Prompt disappearance of the organisms from the oral and pharyngeal lesions followed, and healing of oral ulcerations was rapid except in the presence of other oral pathology, such as carious teeth.

Fusospirochetal organisms frequently appear in the pharyngeal lesions of infectious mononucleosis; approximately 8% of our cases revealed an increase of fusospirochetal organisms in the pharyngeal ulcerations. Aureomycin and penicillin therapy cause these secondary organisms to decrease in

number and they frequently disappear from the lesions. Little influence on the basic pathology, however, is apparent from removal of these bacteria. This situation resembles the role of fusospirochetal invasion of the buccal membranes as an agent secondary to such other pathological conditions as vitamin deficiencies or carious teeth.

Discussion. During the past year reports published by Brainerd *et al.*[2], Gruskin[5], Lyons[8], Woodward *et al.*[15] Wright *et al.*[16], and Seifert *et al.*[12] have indicated the possible therapeutic value of aureomycin in the treatment of infectious mononucleosis. Both clinically and in apparent therapeutic effect, many cases reported in these papers are matched by similar cases in the present series. Our own cases that appear to support the idea of therapeutic effectiveness of aureomycin, however, not only correspond in considerable detail with those cited in the literature, but also correspond in equally full detail with many of our untreated cases. Obviously the evaluation of any therapy in infectious mononucleosis continues enigmatic.

Adequate evaluation of therapy in this disease is hampered seriously by inability to correlate the several components of the clinical and laboratory picture. The picture in many of our control cases could be superimposed easily upon that of the treated cases.

The comparison outlined in Table 1 represents an attempt to evaluate response to treatment on the basis of duration of hospitalization as a possible index of therapeutic effect. Such an index at least includes the various phases of the clinical aspects of mononucleosis. This criterion certainly reveals no significant statistical difference in favor of aureomycin therapy. The evidence may not be sufficient to support a negative verdict, but it deserves consideration.

Toxicity. Two groups of toxicity reactions appear in this study: those patients who received aureomycin prior to November 1949 and those studied after that date. The former group manifested toxic effects in 14 (87%) out of 16 cases. The major manifestations were gastrointestinal in type with nausea, vomiting, diarrhea, abdominal cramps, and rectal burning; in all such cases these effects led to discontinuance of therapy after the first 48 or 72 hours. After 1949, however, the aureomycin received for this study had been definitely improved. Since then toxic manifestations have been uncommon and those that appeared were mild. In the 16 cases treated with the newer type of aureomycin there were no toxic manifestations sufficient to require discontinuance of the treatment.

Conclusions. 1. Thirty-two patients with proved infectious mononucleosis were treated with aureomycin, 2 gm. daily in divided doses for periods of from 2 to 8 days. Thirty patients were maintained untreated as controls.

2. Aureomycin showed no apparent therapeutic effect on the usual type of pharyngeal-glandular mononucleosis.

3. Aureomycin promptly eliminated fusospirochetal organisms from infectious mononucleosis oro-pharyngeal lesions.

4. In 2 cases of mononucleosis associated with pneumonitis definite therapy effects resulted from aureomycin.

5. Since November, 1949, only mild toxic symptoms have appeared in connection with the aureomycin used in this study.

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CORRELATION OF ELECTROCARDIOGRAPHIC AND PATHOLOGIC FINDINGS IN RING-LIKE SUBENDOCARDIAL INFARCTION OF THE LEFT VENTRICLE*†

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In a pioneer study of experimental myocardial infarction in dogs, Wilson *et al.*[18] demonstrated a close correlation of the QRS and RS-T patterns in multiple direct and precordial leads with the distribution of the infarct through the subjacent myocardium and delineated 3 concentric zones in large lesions: 1) a central zone of transmural infarction, manifested by an abnormal QS deflection; 2) a marginal zone of subendocardial infarction, marked by an abnormal QR complex; 3) an outlying zone of ischemia accompanied by changes in the RS-T segment and T wave, but not in the QRS pattern.

Upon application of Wilson's criteria to the interpretation of multiple thoracic leads in man, good correlation between electrocardiographic and pathologic findings can usually be obtained in the presence of transmural or subendocardial infarcts, involving part of the circumference of the left ventricle[8-14]; however, relatively little attention has been devoted to the comparatively rare lamellar infarcts extending around the entire circumference. Isolated cases of ring-like subendocardial infarction, explored by multiple precordial leads, have been reported, 2 in our previous series (Cases 38[8] and 66[9]), 2 by Levine and Ford[2] (Cases 1 and 2), and 1 by Yu and Stewart[19] (Case 7). The electrocardiograms in these cases showed acute RS-T depression referable to subendocardial injury, but generally no diagnostic QRS patterns.

The purpose of this report is to analyze the electrocardiographic findings in patients with pathologic evidence of ring-like subendocardial infarction, extending around the entire circumference of the left ventricle, but confined essentially to the subendocardial half of the free wall and to the left side of the septum, as illustrated in Figs. 1 and 4. The method of electrocardiographic and pathologic study has been described elsewhere[13]. The material comprises 15 cases, including the 2 published cases cited above and 13 previously unreported.

Pathologic Findings. The involvement of the entire circumference of the left ventricle and limitation essentially to the subendocardial half of the outer wall and left half of the septum were found grossly and confirmed by microscopic examination. The ring-like

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distribution was continuous from apex to base in 6 of the specimens; it was demonstrable in the apical two-thirds or more in 7 additional hearts, and in the apical third or more of the left ventricle in the 2 remaining. The findings were classified according to age of the lesion into the following 4 groups: entirely recent, 5 cases; predominantly recent, but partially old, 5 cases; predominantly healed, but with recent reinfarction, 1 case; entirely healed, 4 cases. In every case of the first 2 groups, histologic study demonstrated diffuse infarction of approximately the subendocardial half of the free wall and left side of the septum in all microscopic blocks, or at least in the majority of sections with large confluent patches of infarction in the remaining blocks. In the last 2 groups, the subendocardial half of the free wall and left side of the septum appeared to be replaced by fibrous tissue on gross examination, but showed small scattered islands of intact muscle on microscopic study. The fact that the infarction was distributed either diffusely or in large confluent patches throughout the entire subendocardial layer differentiated the cases in this series from those with localized miliary infarction, described by Lisa and McPeak[3], and from those with focal myomalacia, described by Master and associates[7].

Identification of individual muscle bundles could not be made grossly in any of the specimens, perhaps because the hearts were sectioned into transverse slices. Utilizing the anatomic descriptions of Robb and Robb[16] and Lowe and Wartman[4,5], it was concluded that the infarction was not limited to a single muscle bundle in any case. The subendocardial divisions of the superficial sinospiral and superficial bulbospiral muscles, the scroll muscle, and portions of the deep bulbospiral muscle were apparently involved in all cases, and the posterior part of the deep sinospiral muscle was infarcted in 3 cases.

Occlusion of one or more major coronary arteries was found in 5 cases; marked narrowing of all major branches, without complete occlusion, was present in 8 cases; mild to moderate narrowing, without occlusion, was present in the 2 remaining cases. Myocardial infarction was apparently precipitated in the latter patients by peripheral circulatory collapse from massive gastrointestinal hemorrhage and pancreatitis, respectively.

Clinical Findings. The only noteworthy clinical features of acute ring-like subendocardial infarction was an apparently greater incidence and severity of circulatory collapse than in acute infarction localized to a portion of the circumference. Six of the 11 patients observed during the acute stage were in profound shock; the remainder exhibited a moderate to mild degree of shock. Accessory factors that apparently contributed to the shock and myocardial lesion[1,6] included gastrointestinal hemorrhage in 2 cases, peripheral embolism in 1 case, pancreatitis in 1 case, and dehydration from diarrhea in 1 case.

One of the patients with healed circumferential subendocardial infarction had been free of cardiac symptoms and died of mesenteric thrombosis; the other 3 had angina pectoris, and 2 of these died of intractable congestive failure and 1 of pneumonia.

Electrocardiographic Findings. QRS Complex. On the basis of QRS patterns, the cases were classified into the following 5 groups:

1. *QRS patterns diagnostic of infarction of both the subendocardial aspect of the free wall and the septum* were present in 1 case of recent infarction and 2 cases of healed infarction. The

electrocardiographic features are exemplified by Fig. 1.

The findings were considered diagnostic of infarction of the subendocardial aspect of the free wall when either of the following patterns was recorded in unipolar leads facing the left ventricular surface: (a) QR complex, characterized by an initial downstroke, measuring 0.03 second or longer

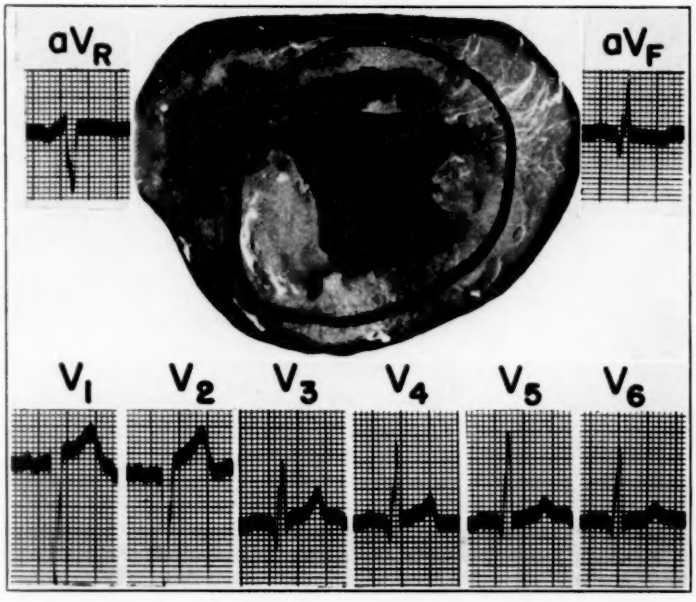

FIG. 1.—The electrocardiogram reproduced in this illustration was obtained on a man, 72 years of age, 5 days before death from cerebral hemorrhage. The patient gave a history of myocardial infarction 10 years previously with subsequent angina of effort, and first came under our care 1 year ago because of a prolonged bout of retrosternal pain. The QRS patterns at that time were comparable to those in this illustration, whereas the RS-T changes in serial curves were consistent with acute subendocardial injury. No cardiac glycosides were given during either hospitalization.

The accompanying photograph reproduces a roentgenogram of a transverse section of the injected heart, 3 cm. above the apex, and is mounted with the anterior surface downward. Gross and microscopic examination revealed a healed ring-like infarction of the subendocardial half of the entire left ventricle with a mural thrombus attached to the left side of the septum, as outlined in the illustration. The infarct was similar in distribution in the remainder of the apex, but was not completely circular in the basal half.

The abnormal duration of the Q waves in leads V_3, V_4, V_5, and V_6, together with the notching or slurring of the ascending limb of the R wave, was diagnostic of infarction of the subendocardial aspect of the anterior and lateral walls. Although the Q wave in lead aV_F was within normal limits in duration, the coarse notching of the succeeding upstroke, together with the Q/R ratio of 37%, indicated that the QR complex was diagnostic of subendocardial infarction and referable to continuation of the lesion into the posterial wall. The minute upstroke and broad slurred S wave in leads V_1 and V_2 signified that the electrode in these positions reflected chiefly the potential variations of the right ventricle and right side of the septum. Upon careful scrutiny, a small, but distinct, initial Q wave was detected in both leads and led to the diagnosis of infarction of the left side of the septum. The diagnostic significance of this QRS pattern has been brought out previously[5], and the probable derivation is discussed in the comments on Fig 3. The RS-T patterns in the precordial leads were consistent with the healed lesion found at autopsy.

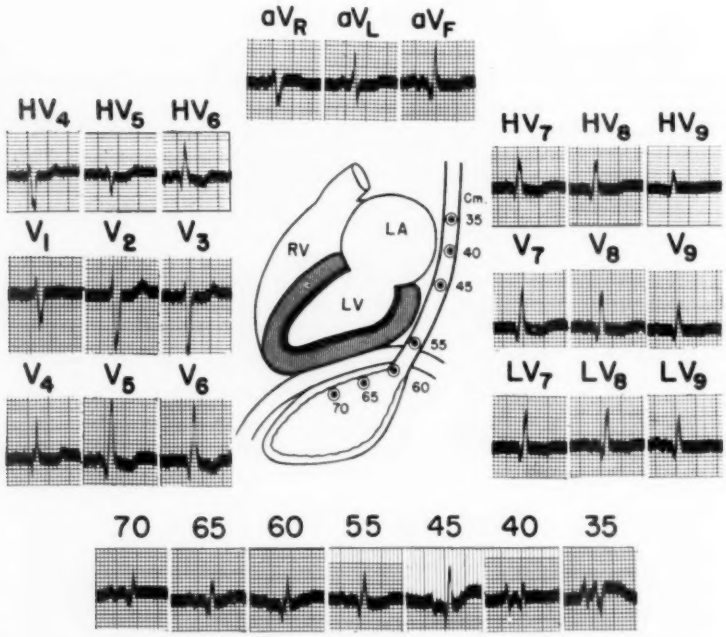

FIG. 2.—Electrocardiogram obtained about 1 year after myocardial infarction in a man, 62 years of age, maintained on digitalis. Multiple leads from precordium, back, and esophagus are reproduced to illustrate their value in delineating the full extent of the infarct. HV leads were taken at the intersections of a horizontal line at the level of the sternal end of the third interspace with vertical lines through the customary electrode positions; LV leads were taken in the left lumbar region, below the diaphragm; approximate anatomic position of gastric and esophageal leads is indicated in the diagram, the numbers representing the distance in centimeters from electrode to the nares.

The heavy black line in the sagittal section of the left ventricle represents the position of a healed sheet-like subendocardial infarct predicted from the QRS patterns and subsequently confirmed at autopsy. The basal third of the septum was intact and was presumably responsible for initial negativity of the left ventricular cavity and thus the Q waves recorded in leads facing the outer wall of the left ventricle. The abnormal QR complexes in leads V_4, V_5, V_6, and V_7 were referable to subendocardial infarction in the apical portion of the anterior and lateral walls of the left ventricle; the similar pattern in HV_6 and HV_7, to continuation into the basal portion of the lateral wall.

The QR complexes with broad notched Q waves, recorded in leads from the stomach (70 and 65), the left leg (aV_F), and lumbar region, LV_7, LV_8, and LV_9, were referable to subendocardial infarction of the diaphragmatic portion of the posterior wall of the left ventricle; the QR complexes recorded in leads from the lower esophagus (60 and 55) differed in that the notch was inscribed on the upstroke of the R wave rather than the apex of the Q, but were likewise diagnostic of subendocardial infarction and, along with the patterns in back leads V_8 and HV_8, were referable to continuation of the lesion into the basal portion of the posterior wall of the ventricle. Leads V_1, V_2, V_3, HV_4 and HV_5 reflected chiefly the potential variations of the right ventricle and right side of the septum and revealed no evidence of the infarction of the apical two-thirds of the septum found at autopsy.

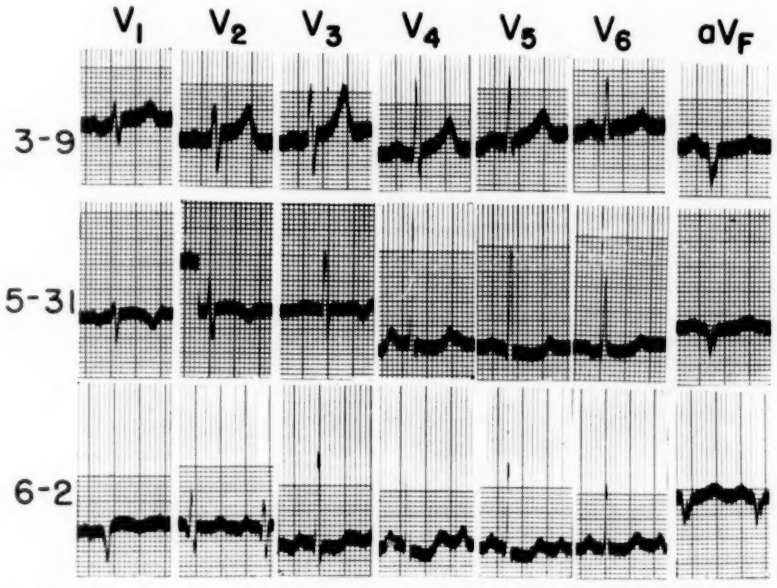

FIG. 3.—Serial electrocardiograms obtained on a man, 65 years of age, who had been under our care 10 years previously because of posterior infarction. The tracing of March 9 was taken as a routine prior to resection of a gastric carcinoma. The heart was in horizontal position and the QS deflection in lead aVF was attributable to infarction of the posterior portion of the septum[6], whereas the exaggerated R and T waves and diminutive S waves in right precordial leads were considered reciprocal to infarction of the posterior wall of the left ventricle. The precordial leads of this tracing showed no evidence of anterior or lateral infarction.

Convalescence was uneventful until May 30, when the patient was awakened by severe retrosternal pain that lasted for 8 hours. The tracing of May 31, obtained 34 hours after the onset of the pain, showed sagging of the RS-T segments in leads V_4 and V_5, attributable to acute injury of the subendocardial aspect of the anterolateral wall of the left ventricle and reversal in the direction of the T waves in V_1, V_2 and V_3, compatible with extension of the injury into the septum. The absence of significant change in the QRS pattern over that recorded on March 9 was consistent with either a patchy injury or a very early injury, too recent for obliteration of the response to the activating impulse.

The pain recurred on June 1 and the last tracing was obtained about 24 hours later. The most significant change occurred in the right precordial leads and was characterized by replacement of the RS in V_1 by a QS deflection, and the appearance of an abnormal Q wave in leads V_2 and V_3, indicating the development of initial negativity of the right ventricular cavity as a result of activation of a considerable portion of the septum in a right to left direction. This was interpreted as evidence of infarction of the left side of the septum; however, a portion of the septum was spared and activated in the usual left to right direction, as shown by the persistence of small q waves in left precordial leads V_4, V_5 and V_6. In spite of the absence of significant change in the QRS pattern in left precordial leads, further injury to the subendocardial aspect of the anterolateral wall occurred, as shown by the increasing RS-T depression in leads V_4 and V_5. No cardiac glycosides were given at any time. Death occurred on June 4.

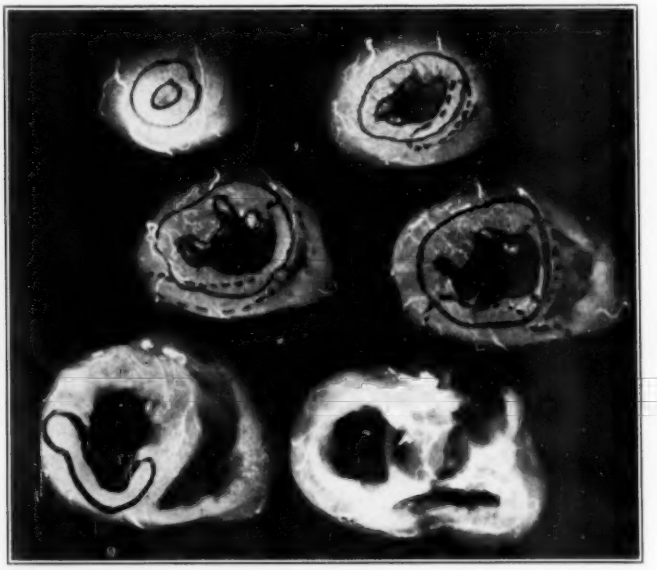

FIG. 4.—Roentgenogram of the injected heart from the patient in Fig. 3, sectioned into tranverse slices 1 cm. in thickness and mounted with anterior surface downwards. Position of the healed posteroseptal infarct is indicated by broken lines; boundaries of the recent ring-like subendocardial infarct are delineated by solid lines.

Microscopic examination demonstrated diffuse infarction within the area demarcated by solid lines and absence of infarction of the subepicardial laver. The septal portion of the healed infarct accounted for the QS pattern consistently recorded in lead aVF; the posterior portion of the healed infarct was responsible for the reciprocal exaggeration of the R and T waves of right precordial leads in the first tracing. The recent infarction of the left side of the septum accounted for the development of abnormal Q waves and for the RS-T displacement in right precordial leads. The recent infarct of the subendocardial aspect of the anterolateral wall of the left ventricle was responsible for the acute RS-T depression in left precordial leads and was of sufficient duration and density to have led one to expect changes in the QRS pattern, as well.

The failure of the pre-existent Q waves in leads V_4, V_5, and V_6 to increase in depth or duration was attributed to the uniform distribution of the infarct around the entire circumference of the left ventricle, leaving little or no intact muscle in the subendocardial aspect of the opposite (posterior) wall to be activated early and thus to serve as a source for the negative potentials recorded as an abnormal Q wave in leads facing the anterolateral portion of the infarct.

from onset to nadir and more than 25% of the amplitude of the succeeding R wave, as illustrated by leads V_3 and V_4 of Fig. 1 and by leads E_{70} and E_{65} of Fig. 2; (b) QR complex, characterized by definite notching of the upstroke of the R wave and a distinct antecedent Q wave, which need not comply with the above measurements, as illustrrted by lead aVF of Fig. 1 and by leads E_{60} and E_{55} of Fig. 2.

In the patient with the recent infarct, the septal portion of the lesion was diagnosed from the registration of an abnormal initial Q wave and prominent late R wave in right precordial leads, in the presence of a QRS interval of 0.14 second[10]. In the 2 cases with a healed infarct, the septal portion of the lesion was recognized from

the registration of a qrS complex* of less than 0.12 second duration in the same leads, the q wave indicating initial negativity of the right ventricular cavity from early activation of the septum in a right to left direction, consequent upon infarction of the left side of the septum[10].

2. *QRS patterns diagnostic of infarction of the subendocardial portion of the free wall, but not the septum,* were present in 2 cases with acute infarction, 2 with a recent lesion superimposed on an old lesion, and 1 with an entirely healed lesion. The electrocardiograms of the latter case are reproduced in Fig. 2 to illustrate the wide distribution of the abnormal QR patterns in leads from the back, lower esophagus and stomach, as well as the left precordium, and the close correlation with the extensive ring-like subendocardial infarct found at autopsy. Abnormal QR complexes, roughly comparable in configuration, were recorded in all leads facing the subendocardially infarcted anterior, lateral, and posterior walls of the left ventricle in only 2 of the 8 cases in Groups 1 and 2. In the remaining 6 cases, abnormal QR complexes were found in leads facing portions of the ventricle where the subendocardial infarct was thickest or most dense, whereas borderline to normal qR patterns were recorded in leads from portions of the ventricle where the infarct was thinner or more patchy.

3. *QRS patterns diagnostic of infarction of the septum, but not of the free wall,* were present in 1 case of recent superimposed on healed infarction. The electrocardiographic and pathologic findings in this patient are illustrated and discussed in Figs. 3 and 4.

4. *Incomplete left bundle branch block* was present in 5 cases and could be correlated with pathologic evidence of infarction of the left side of the septum, which was classed as acute in 2 cases, partly recent and partly old in 2, and entirely healed in 1. Nevertheless, the QRS pattern of incomplete left bundle branch block can be regarded merely as compatible with septal infarction, rather than pathognomonic, inasmuch as it has been observed in many cases without evidence of septal infarction at autopsy. As a result of the incomplete left bundle branch block, initial R waves were recorded in all leads facing the epicardial surface of the left ventricle, thereby obscuring evidence of the infarction of the subendocardial aspect of the outer wall, demonstrated at autopsy. The ascending limb of these R waves was usually notched or coarsely slurred, but not necessarily so, as exemplified by the case in Fig. 5. The combination of QRS patterns of incomplete left bundle branch block with RS-T depression and QT prolongation typical of acute subendocardial injury, as illustrated in Fig. 5, was observed in 3 patients of this group who had received no cardiac glycosides, and was considered strongly suggestive, though not pathognomonic, of the acute ring-like subendocardial infarct found at autopsy. RS-T depression was also present in the tracings of the other patient with recent subendocardial infarction, but could not be considered of diagnostic significance because of the prior administration of digitalis.

5. *Normal QRS pattern* was found in 1 patient (Case 38 of a previous series[8]), apparently because of the early recording of the electrocardiogram, before progression of the myocardial injury to the point of obliteration of response to the activating impulse would have been expected. A

* The lower case letters are used to denote a deflection of relatively small amplitude; the upper case letters, to indicate a deflection of relatively large amplitude.

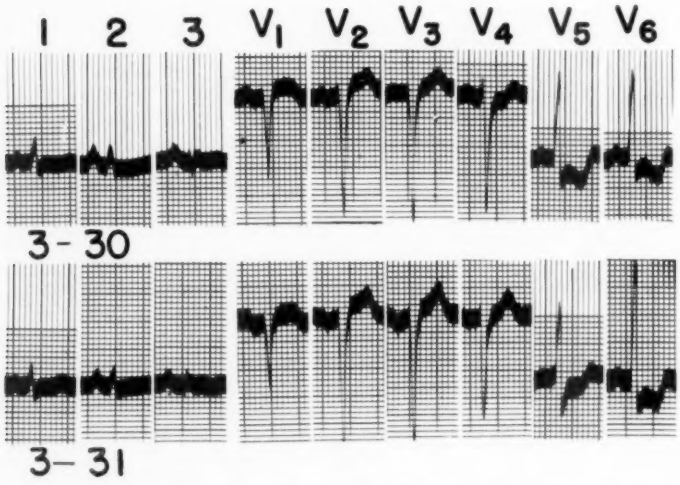

FIG. 5.—The tracings were obtained on a man, 64 years of age, who was seized with crushing retrosternal pain and dyspnea on March 27 and was admitted in profound shock on March 29. No cardiac glycosides were given before or during hospitalization. Death occurred 19 hours after the last electrocardiogram.

The first 4 precordial leads of both tracings reflected chiefly the potential variations of the right side of the septum and right ventricle; the last 2, those of the left side of the septum and the left ventricle. The increasing depression of the RS-T junction in lead V_6, along with the straight downslope of the RS-T segment and inversion of the T, as well as the changing RS-T pattern in lead V_5, were interpreted as evidence of acute injury of the subendocardial aspect of the anterolateral wall of the left ventricle, inasmuch as the possibility of a digitalis effect had been excluded. The absence of a Q wave from left ventricular leads V_5 and V_6, together with the QS complex recorded in right ventricular leads V_1, V_2, and V_3, indicated that the septal vector was directed from right to left and, when taken in conjunction with the QRS duration of 0.10 second, led to a diagnosis of incomplete left bundle branch block. The fact that the upstroke of the initial R waves in leads V_5 and V_6 was only slightly slurred, rather than coarsely notched, did not invalidate this conclusion, since Sodi-Pollares *et al.*[17] obtained simultaneous records from the right and left ventricular cavities, proving the presence of incomplete left bundle branch block in patients with comparable QRS patterns in left precordial leads. The small initial R wave in lead V_4, taken from a point just to the right of the transitional zone, could not be explained by early activation of the anteroseptal wall of the right ventricle. In the interpretation of the tracing, the incomplete left bundle branch block was regarded as consistent with, but not diagnostic of, infarction of the left side of the septum. The bipolar limb leads showed low voltage of both QRS and T, but yielded no direct or indirect evidence of the infarction found at autopsy.

The pathologic findings were so much like those in the case illustrated in Fig. 4 that the roentgenogram of the injected heart was not reproduced. An old healed posteroseptal infarct was found, compatible in distribution with that in Fig. 4. In the apical three-fourths of the left ventricle, a recent ring-like infarct was found, confined to the subendocardial half of the free wall and left side of the septum, and was almost identical in distribution with that in the corresponding segments of Fig. 4. The incomplete left bundle branch block could be correlated with the septal portion of the infarct, but interfered with the registration of QRS patterns diagnostic of the infarction of the subendocardial aspect of the free wall. The RS-T changes in leads V_5 and V_6 were an expression of the acute subendocardial injury from the lesion in the anterolateral portion of the wall.

normal QRS pattern is also likely when the infarct is distributed in discrete patches, surrounded by preserved myocardium, but cases of this type were eliminated from this series by the method of selection.

RS-T Segment and T Wave. The analysis of the RS-T pattern will be restricted to the 7 patients who had received no cardiac glycosides prior to registration of the electrocardiogram and had evidence of recent subendocardial infarction at autopsy. The QT interval was prolonged in all cases. Elevation of the RS-T segment in lead aVR, a recognized manifestation of acute subendocardial injury[15], was found in only 3 cases and was accompanied by an abnormal upright T wave in 2 and an inverted T wave in 1. Abnormal depression of the RS-T junction was present in left ventricular leads of 5 cases and was generally accompanied by downward sagging of the RS-T segment, as exemplified by leads V_4 and V_5 of the tracing of June 2nd in Fig. 3, and by leads V_5 and V_6 of Fig. 5. The abnormal RS-T segment was followed by either a diphasic T wave, as in leads V_4 and V_5 of the tracing of June 2 in Fig. 3, or an inverted T wave, as in V_6 of Fig. 5. These findings were considered typical of acute subendocardial injury. An electrocardiogram of the sixth patient exhibited abnormal RS-T depression in leads V_4, V_5 and V_6, which was well correlated with infarction limited to the subendocardial half of the anterior and lateral walls, but showed a slightly elevated, dome-shaped RS-T segment in aVF, referable to subepicardial injury and correlated with edema and cellular infiltration on the subepicardial aspect of the posterior wall. This merely exemplifies the fact that coexistent subepicardial injury obscures the characteristic effects of recent subendocardial infarction on the RS-T pattern. The seventh patient had right bundle branch block, due to septal infarction, with slightly elevated RS-T segments and cove negative T waves in right precordial leads, presumably referable to the septal injury.

Summary. An analysis has been made of the electrocardiographic findings in 15 patients with pathologic evidence of confluent ring-like infarction confined essentially to the subendocardial half of the free wall of the left ventricle and the left side of the septum. Abnormal QR complexes, diagnostic of subendocardial left ventricular infarction, were found in 8 cases; QRS patterns, diagnostic of septal infarction, were present in 3 of the foregoing and in 1 additional case; incomplete left bundle branch block compatible with septal infarction was encountered in 5 cases. The classical RS-T pattern in recent subendocardial infarction was characterized by depression of the RS-T junction, downward sagging of the segment, and a diphasic to inverted T wave.

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SERUM LIPID STUDIES IN EUTHYROID SUBJECTS FOLLOWING THE ADMINISTRATION OF THYROID

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DISTINCTIVE serum lipid changes have been described during the therapy of hypothyroid patients with thyroid preparations[9,24]. Our observations of euthyroid subjects treated with thyroid disclose a completely different pattern of serum lipid changes. The highest total daily level of thyroid administered to these patients was 2½ grains, and this amount was achieved by slowly increasing (bimonthly) the daily medication. Great caution was necessary because the majority of these subjects were experiencing angina pectoris secondary to coronary atherosclerosis. All subjects were chosen upon the premise that they 1) had normal thyroid function and 2) showed objective and subjective evidence of atherosclerotic involvement of the coronary vessels or of the arterial tree of the lower extremities. All were placed upon a low fat, low cholesterol diet.

Methods and Material. Fifteen euthyroid patients, 12 males and 3 females, were studied. The ages of the 12 men varied between the extremes of 37 and 67 years of age, the average age being 52.7. The ages of the 3 women were 43, 44, and 52, the average being 46 years of age. The average duration of therapy was 7.3 months. In each case a complete history was taken and physical examination (combined with laboratory data) was done and evaluated in the consideration of thyroid function. Two of these patients, both men, showed the signs and symptoms of intermittent claudication secondary to atherosclerotic involvement of the vessels of the lower extremities. The other 13 subjects who were studied had involvement of the coronary vessels. For acceptance the patient was required to show regularly both objective and subjective evidence of vessel involvement. This meant that pain with classical radiation was present often enough to be classified as following a certain chronological schedule. It meant also that an abnormal exercise electrocardiogram was present in the group experiencing anginal discomfort and that abnormal reflex vasodilation changes were found in the patients with intermittent claudication. The skin temperatures, before and after application of heat to the upper extremities, were measured under basal conditions in a special room kept at 66° F. The Rauh surface pyrometer was used. Cholecystograms were done in 11 cases and roentgen studies of the cervical spine in a minority. A battery of liver function tests was done initially and consisted of determinations of the thymol turbidity, icterus index, cephalin flocculation, and the cholesterol ester/cholesterol ratio. In this initial workup we included a complete blood count, urinalysis, and determination of blood uric acid and urea clearance. Fluoroscopy of the chest was done in some patients. During therapy the basal metabolic rates were done as in-

TABLE 1.—SERUM LIPID DETERMINATIONS IN 15 EUTHYROID SUBJECTS

Case No.	Date	C	CE	LP	NF	TL	Date	C	CE	LP	NF	TL	Date	C	CE	LP	NF	TL
Group A																		
1 B. F.	4/27/50	234	146	4.6	42	571							11/21/50	240	168	5.6	85	832
2 C. L.	4/20/50	385	260	10.5	0	940	10/6/50	416	328	11.0	28	1320	1/12/50	400	315	11.5	59	1150
3 D. J.	12/28/50	317	219	9.6	127	952	4/1/50	392	265	13.6	0	976	1/5/51	294	212	10.9	85	1035
4 E. F.	7/3/50	240	160	7.0	65	724	9/1/50	291	195	8.1	73	891	1/5/51	221	162	11.2	74	792
6 I. E.	4/1/50	368	231	14.2	405	1425	4/25/50	556	366	22.4	1213	2878	1/9/51	236	154	13.6	338	1150
7 L. A.	5/4/50	353	239	9.7	17	931	7/19/50	398	238	9.2	82	918	12/15/50	248	177	12.6	8	808
9 O. H.	5/16/50	378	275	8.6	204	1115	7/15/50	387	254	13.0	164	1365	12/16/50	293	208	10.2	100	1105
10 P. E.	4/4/50	343	244	9.0	25	862							10/20/50	338	236	9.2	59	969
12 R. A.	4/19/50	303	250	5.9	66	950							10/20/50	280	209	10.5	0	896
15 W. S.	3/13/50	301	157	5.5	42	900	6/24/50	288	191	10.5	0	752	10/31/50	298	222	8.9	0	954
Avg.		322	218	8.46	99	937								284	206	10.4	90	969
Group B																		
5 F. C.	4/1/50	316	201	11	0	800							10/20/50	351	264	12.1	34	1040
8 M. M.	5/1/50	234	142	10.0	65	862	6/17/50	203	119	8.0	99	884	10/25/50	264	184	7.1	168	985
11 P. C.	1/11/50	246	171	11.0	263	1005	5/3/50	284	188				10/27/50	309	236	9.8	111	942
14 T. W.	1/27/50	253	179	9.6	0	841	4/22/50	279	181	8.1	34	776	10/10/50	363	202	7.5	200	1079
Avg.		262	173	10.4	82	877								306	221	9.13	128	1011

GROUP A, FALL IN TOTAL CHOLESTEROL/PHOSPHOLIPID (C/P) RATIO; GROUP B, RISE IN C/P RATIO*

* C, Total Cholesterol; CE, Cholesterol Esters; LP, Lipid Phosphorus; NF, Neutral Fat; TL, Total Lipids.
All values expressed as mg. per 100 cc. of serum.

dicated. The modified Masters' double two-step exercise test[19,20,27,34,35] and a resting electrocardiogram and ballistocardiogram were made in each case before, after, and occasionally during therapy. Complete post-absorptive blood fat analyses were made before and during the period of observation. The methods used are as follows: for cholesterol and cholesterol esters, Bloor and Knudson[4]; for fatty acids, Stoddard and Drury[29]; for lipid phosphorus, Youngburg and Youngburg[33], using the method of Fiske and SubbaRow[7]. The total lipids were determined gravimetrically according to the method of Rubin[26]. Each patient was placed upon a low cholesterol–low fat diet. For those patients who were overweight (normal standards used were those of Davenport[6A]) a low-caloric dietary regimen was instituted. The medicinal therapy consisted of drugs in these daily amounts: choline dihydrogen citrate, 12.66 gm.; inositol, 4 gm.; pyrodoxine hydrochloride, 60 mg.; riboflavin, 30 mg.; niacinamide, 360 mg.; ascorbic acid, 300 mg.; and thiamin chloride, 60 mg.* The total daily thyroid dose varied between ½ and 2½ grains. We began with the smallest dose and increased the amount over a period of months by adding ¼ to ½ grain every 2 to 4 weeks. Some patients were given phenobarbital, grains 1/6 three times a day as a mild sedative. In order to compare the results obtained, each patient is consistently referred to throughout the article and in all charts by the same case number.

Results. Serial cholesterol determinations give only a partial picture of the patient's blood lipid status. The physical state of the blood lipids is of prime importance in the characterization of the serum lipid state[14,16,17]. Because of their role as a stabilizing influence upon serum lipids[2,25] the phospholipid determinations were of great interest to us. We determined, therefore, not only the actual lipid levels, but also the relationship between the 1) total cholesterol and phospholipids[1,22] and 2) total lipids and phospholipids. These ratios are re-

* Courtesy of Vascular Pharmaceutical Co., New York, New York.

corded in Tables 1, 2, and 3 as C/P and TL/P.

The average serum total cholesterol level in the 13 patients with angina pectoris was 299 mg. per 100 cc., and this is characteristically higher than in patients in a similar age group with no atherosclerotic involvement of the coronary vessels[12]. Following therapy the average serum total cholesterol in these patients was 298 mg. per 100 cc. Serum cholesterol levels may be extremely labile in patients with coronary atherosclerosis[21,28], moving either in an upward or downward direction. Therefore we considered cholesterol changes significant only if they were of relatively large magnitude. Based upon the conclusions of others[28], we chose a minimum change of 20% of the original determination as a significant difference. It is evident that 10 of the 15

TABLE 2.—SERUM LIPID RATIOS IN 15 EUTHYROID SUBJECTS

GROUP A, FALL IN TOTAL CHOLESTEROL/PHOSPHOLIPID (C/P) RATIO; GROUP B, RISE IN C/P RATIO*

Case No.	*Date*	*C/P*	*TL/P*	*CE/C*	*Date*	*C/P*	*TL/P*	*CE/C*	*Date*	*C/P*	*TL/P*	*CE/C*
GROUP A												
1 B. F.	4/27/50	2.03	4.91	.67					11/21/50	1.71	5.9	.70
2 C. L.	4/20/50	1.46	3.5	.67	10/6/50	1.51	4.8	.78	1/12/51	1.38	4.0	.788
3 D. J.	1/28/50	1.32	3.9	.69	4/1/50	1.15	2.87	.676	1/5/51	1.17	3.80	.721
4 E. F.	7/3/50	1.37	4.13	.66	9/1/50	1.40	4.38	.670	1/5/51	.79	2.80	.734
6 I. E.	4/1/50	1.03	4.02	.629	4/25/50	.99	5.13	.654	1/9/51	.69	3.80	.653
7 L. A.	5/4/50	1.45	3.8	.67	7/19/50	1.37	3.9	.72	12/15/50	.786	2.5	.71
9 O. H.	5/16/50	1.75	5.18	.729	7/15/50	1.18	4.2	.657	12/16/50	1.15	4.3	.710
10 P. E.	4/6/50	1.52	3.8	.710					10/20/50	1.47	4.1	.700
12 R. A.	4/19/50	2.02	6.3	.82					10/20/50	1.06	3.4	.84
15 W. S.	3/18/50	2.19	6.57	.52	6/24/50	1.09	2.86	.68	10/31/50	1.34	4.2	.74
AVG.		1.61	4.61	.675						1.15	3.88	.719
GROUP B												
5 F. C.	4/1/50	1.14	2.8	.636					10/20/50	1.16	3.4	.752
8 M. M.	5/1/50	.920	3.4	.603	6/17/50	1.01	4.4	.590	10/25/50	1.48	5.56	.698
11 P. C.	12/11/50	.895	3.6	.69	5/3/50			.662	10/27/50	1.26	3.8	.76
14 T. W.	1/27/50	1.05	3.5	.71	4/22/50	1.36	3.78	.65	10/10/50	1.61	5.73	.66
AVG.		1.00	3.33	.659						1.38	4.62	.7175

* TL/P, Total Lipids/Phospholipid; CE/C, Cholesterol Esters/Total Cholesterol. All values are expressed as mg. per 100 cc. and phospholipids are expressed as lecithin or 25 × lipid phosphorus determination.

TABLE 3.—LIPID RATIOS IN 15 EUTHYROID SUBJECTS BEFORE AND AFTER THERAPY. SUMMARY OF CHANGES

GROUP A, FALL IN TOTAL CHOLESTEROL MG. PER 100 CC./PHOSPHOLIPID MG. PER 100 CC. RATIO (C/P) *i. e.*, FAVORABLE TREND.

GROUP B, RISE IN C/P RATIO, *i. e.*, UNFAVORAPLE TREND*

Case No.	*C/P Ratio*	*Total Cholesterol*	*Lipid Phosphorus*	*Cholesterol Esters Total Cholesterol*	*Total Lipids Phospholipids*	*Weight (lbs.)*	*Symptoms*
GROUP A							
1 B. F.	−.32	+6	+1.0	+.03	+1.0	L	I
2 C. L.	−.08	+15	+1.0	+.11	+.50	NC	I
3 D. J.	−.15	−23	+1.3	+.03	−.10	NC	NC
4 E. F.	−.58	−19	+4.2	+.07	+1.33	L	I
6 I. E.	−.34	−132	−.6	+.03	−.22	L	I
7 L. A.	−.67	−105	+2.9	+.04	−1.3	L	I
9 O. H.	−.60	−85	+1.6	−.01	−.80	L	I
10 P. E.	−.05	−5	+.2	−.01	+.30	NC	I
12 R. A.	−.96	−23	+4.6	−.08	−2.9	L	I
15 W. S.	−.85	−3	+3.4	−.22	−2.3	NC	NC
AVG.	−.460	−37	+1.96	−.01	−.715		
GROUP B							
5 F. C.	+.02	+35	+1.1	+.12	+.4	NC	NC
8 M. M.	+.56	+30	−2.9	+.09	+2.1	L	I
11 P. C.	+.37	+63	−1.2	+.07	+.2	NC	NC
14 T. W.	+.56	+50	−2.1	−.05	+2.2	NC	I
AVG.	+.377	+44.5	−1.27	+.057	+1.23		

* +, rise; −, fall. Change in ratios expressed as difference between first and last determination. Total cholesterol and lipid phosphorus expressed as mg. per 100 cc. Under weight change: L, significant weight loss; NC, no significant change. Under symptoms: I, improvement; NC, no change.

patients showed no significant change in their cholesterol values during or after therapy. (One patient, Case 13, S.S., is not included in Tables 1, 2, and 3 because in this instance only his total cholesterol levels were computed and they showed a change from 365 to 328 mg. per 100 cc.) Two patients presented a marked fall in their serum cholesterol levels from an average of 373 mg. per 100 cc. to 264 mg. per 100 cc.; and these were the 2 patients with intermittent claudication, Cases 6 (I.E.) and 9 (O.H.). The blood lipids of patients with a) primary essential xanthomatosis of the hypercholesteremic type and b) essential lipemia are peculiarly sensitive to exogenous (dietary) fat restrictions[15,23,30]. Since in Case 6 (I.E.) the serum was grossly lipemic and in Case 9 (O.H.) hypercholesterolemia (with borderline hyperlipemia) and xanthomatous skin lesions were present, it is likely that study of their immediate family members would have revealed stigmata of one of those diseases.

One patient, Case 11 (P.C.), showed a definite rise in serum total cholesterol. Three patients, Cases 5 (F.C.), 10 (P.E.), and 11 (P.C.), showed a significant fall in serum total cholesterol during the first few months of therapy, but the improvement was only transient. (Because of lack of space some of these figures as well as some of the lipid ratio changes are not included in Tables 1, 2, and 3.)

From Tables 2 and 3 it is seen that 10 patients experienced a fall in their C/P ratio, and 4 showed a rise. The TL/P ratio showed a similar rise or fall in all but 3 instances. It is interesting to compare these results with those obtained by Watkins[31] and associates, who studied the blood lipids of patients on a rice diet. In their series a drop in the C/P ratio occurred concomitantly with a sharp decrease in the cholesterol ester fraction and an increased number of abnormal liver function tests. We found no consistent cholesterol ester/cholesterol ratio change in our patients, but one patient, Case 15 (W.S.), showed the opposite effect, that is, a significant rise in the cholesterol ester fraction (Tables 1, 2, and 3). (Liver function tests in our cases were done before but not after therapy; see "Methods". The difference in the magnitude of the phospholipid levels may be accounted for by a difference in laboratory methods[33], but this does not, of course, prohibit comparison of changing trends.) Analysis of the changes in the C/P ratios discloses that in a minority of instances (4) the change was relative, that is, both lipid phosphorus and total cholesterol rose or fell, one more than the other. In the majority of instances, however, an absolute rise or fall in the lipid phosphorus was associated with a total cholesterol level that moved in an opposite direction (Fig. 1). This is unlike the pattern of lipid changes due to weight loss[18] or the treatment of hypothyroidism or hyperthyroidism[9,24], for in these latter 3 clinical states the total cholesterol and lipid phosphorus levels change in the same direction. Peters and Man[24] and Foldes and Murphy[9] emphasize that the hypothyroid individual responds consistently to thyroid therapy with a drop in both serum lipid phosphorus and total cholesterol. Even though relatively large amounts of thyroid were administered in our combined therapy, the majority of our patients showed a rise in lipid phosphorus at least once during therapy. All patients did not show a persistent lipid trend in an upward or downward direction. Fluctuations during the course of therapy reversed transiently the C/P trend, in 5 patients, Cases 2, 3, 4, 7, and 15. It was decided, therefore, to study the diurnal fluctuations

of serum lipid phosphorus and to determine what effect the food intake of the previous day had upon these levels. After a standard fat meal (60 gm. of butterfat for a patient weighing 150 lb. and 5 feet, 10 inches tall), blood specimens were taken during a 24-hr. follow-up period, during which time the patient ingested no fats. The phospholipid variations are pictured in Fig. 2, and they are compared with the concomitant total esterified fatty acid fluctuations. Hirsch and Carbonaro[13] consider the latter to be more informative than cholesterol changes. Like Hirsch and Carbonaro we found

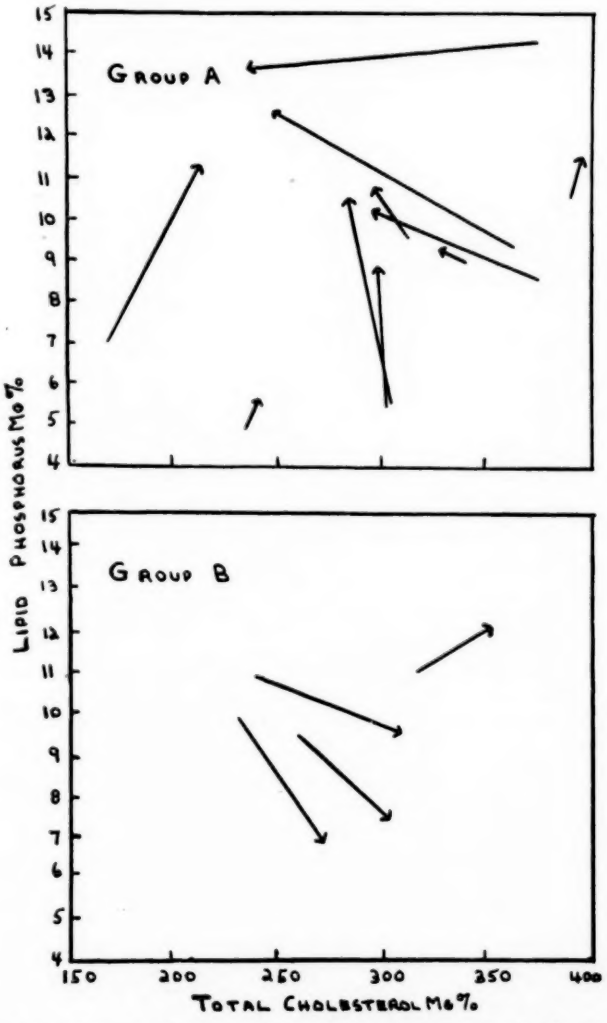

FIG. 1.—Concomitant changes of serum cholesterol and serum lipid phosphorus under this program of therapy. Group A, fall in C/P ratio; Group B, rise in C/P ratio. Tail of arrow indicates the before-treatment levels and the head of each arrow represents the final determination. The 2 fractions showed divergent trends as compared with Fig. 13 of the studies of Watkins and associates[31].

that the total cholesterol did not change significantly. The daily phospholipid variations illustrated in Fig. 2 indicate that wide diurnal fluctuations may occur and that exogenous fat may exert an effect for as long as 24 hours. These changes combined with wide fluctuations of total cholesterol during a period of months may make lipid ratio changes more apparent than real, particularly if the patient is not on a constant dietary regimen or if the observer takes infrequent specimens. (Both thyroid and choline increase the liver and plasma phospholipid turnover[5,8,11], though this may occur without an increase in the plasma phospholipids.)

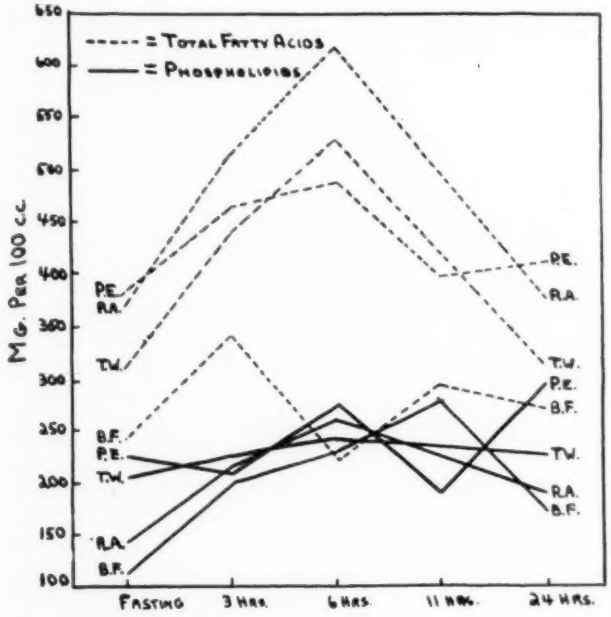

Fig. 2.—Concomitant total fatty acid and phospholipid determinations for a 24-hour period following a standard fat meal. Eleven-hour blood samples were drawn only on patients B.F. and P.E. All 4 patients had coronary atherosclerosis and are discussed in the text.

Discussion. It was most gratifying to find that no undesirable side effects secondary to therapy occurred in any patient. In no instance did the symptoms of the underlying disease (coronary or peripheral vessel atherosclerosis) become worse. There was no significant change in the blood pressure or heart rate during therapy, and the basal metabolic rate showed no elevation. The role that the concomitant administration of choline and inositol played in altering the serum lipid pattern in these patients can be determined only by the separate administration of these agents. Recent studies indicate, however, that it is unlikely that they exerted any significant effects upon the serum lipids[6B]. An inter-reaction in the combined use of thiamin and thyroid[32] and choline and thyroid[10] has been described and warrants further study.

A low caloric diet may be considered to be a lipotropic regimen[3] and the weight loss of each patient is therefore recorded in Table 4. The serum

lipid changes in malnutrition resemble the changes following thyroid therapy in that both cholesterol and lipid phosphorus change in the same direction[18] (a fall), and so the weight changes in our patients cannot in themselves have produced the lipid pattern outlined above. However, the moderate fat and cholesterol dietary restrictions practiced by the patients in this series of atherosclerosis. At the present time, therefore, it cannot be determined if the blood lipid changes described, particularly the C/P ratios, are of a significant enough degree to affect the course of atherosclerosis or if they necessarily indicate a persistent trend. The wide fluctuations which may occur spontaneously in serum lipids (Fig. 2) should cause the observer to

TABLE 4.—WEIGHT CHANGES IN 15 EUTHYROID SUBJECTS

Patient	*Sex*	*Age*	*Thyroid Dose**	*Duration of Symptoms*	*Duration of Therapy*	*Weight††*
Case No. 1, B. F.	M	37	2	1 mo.	8 mo.	−9
Case No. 2, C. L.	F	44	1	6 mo.	5	−4
Case No. 3, D. J.	M	45	2½	1 yr.	10	NC
Case No. 4, E. F.	M	67	½	2 "	6	−14
Case No. 5, F. C.	M	59	2¼	10 "	12	−4
Case No. 6, I. E.	M	53	1½	1 "	7	−17
Case No. 7, L. A.	M	44	1	3 "	7	−23½
Case No. 8, M. M.	M	52	2	8 "	6	−9
Case No. 9, O. H.	M	43	2¼	5 "	7	−17
Case No. 10, P. E.	M	59	2¼	3 "	10	−4
Case No. 11, P. C.	M	53	1⅓	6 "	11	−4
Case No. 12, R. A.	F	52	1½	7 mo.	8	−7
Case No. 13, S. S.	M	64	¾	10 yr.	7	+3
Case No. 14, T. W.	M	57	2¼	5 mo.	8¾	NC
Case No. 15, W. S.	F	43	1	4 "	7¼	NC

* The thyroid dosage is expressed in grains as the highest total daily dose reached during therapy.
†† Weight in pounds: +, gain; −, loss; N.C., no change.

could conceivably produce serum lipid changes (not including cholesterol) distinctly different from more stringent restrictions.

There are recorded comprehensive studies of the wide fluctuations of serum cholesterol in patients with coronary atherosclerosis, but there have been few observations of serum lipid phosphorus changes in the natural course be extremely cautious in stating that serum lipid "improvement" has occurred.

Conclusions. 1. A group of 15 euthyroid subjects with an average age of 51.4 was treated for an average period of 7.3 months with up to 2½ grains of thyroid substance daily. All of these patients had atherosclerotic disease and were regularly experiencing symp-

toms characteristic of either angina pectoris or intermittent claudication.

2. Under this therapy the total cholesterol/phospholipid ratio became lower in the majority of subjects, and this was due predominantly to divergent changes in the cholesterol and phospholipid fractions. This is unlike the lipid pattern found after simple weight loss or after thyroid therapy in hypothyroid subjects. In the latter clinical state, previous reports have stressed that the serum phospholipids consistently fall after thyroid therapy, but the great majority of our euthyroid subjects evidenced a rise in the phospholipid fraction after thyroid was administered.

3. The effect that weight changes and the concomitant administration of other medication may have upon serum lipids is discussed.

4. The wide spontaneous fluctuations of serum lipids is emphasized and it is concluded that it cannot yet be ascertained if the serum lipid changes observed necessarily indicate a persistent trend or if they are of such a degree as to affect the course of atherosclerosis.

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LIPOMICRONEMIA IN MICE CAUSED BY PARENTERAL ADMINISTRATION OF FAT

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The absorption capacity of fats administered parenterally has widespread implications in different branches of medicine, and the absorption has been studied in numerous works using histologic and/or chemical methods. However, the forms in which lipids, introduced parenterally, are carried further in the body are unexplained.

On the contrary, it is known that the physical state in which the main part of the alimentary fats are transported postprandially by the blood stream is that of a finely dispersed chylomicron emulsion[1,4]. Gage and Fish[4] as well as Frazer and Stewart[3] have shown that starvation, under some circumstances, causes a mobilization of depot fat, which occurs in the blood as particles resembling the chylomicrons. These have been called lipomicrons[3].

As far as the authors know, it has not been reported previously that fat, administered parenterally, would appear in the form of visible particles. The present studies, based on observations on mice, show that this may occur.

Methods. Known amounts of different fats and of fat emulsions were injected subcutaneously and intraperitoneally, under aseptic conditions, into adult mice. The subcutaneous injections were made through the skin of the thoracic dorsum into the tissue and included: 1) 0.1 cc. of light petrolatum, 2) 0.1 cc. of olive oil, 3) 0.2 cc. of an emulsion containing 50% of olive oil in distilled water with 5% of pure egg lecithin, and 4) 0.2 cc. of an emulsion containing 50% of olive oil in distilled water with 3% of aqueous sodium cholate solution. The injections made intraperitoneally consisted of: 1) 0.2 cc. of olive oil, 2) 0.2 cc. of an emulsion containing 50% of olive oil in distilled water with 5% of pure egg lecithin, and 3) 0.4 cc. of cow's milk.

Blood samples from the tail vein were taken both immediately before the injection, and 2, 5, 8, and 24 hours later. The number of fat particles in the blood (called lipomicrons in this article) was determined quantitatively with the ultramicroscope technique and was presented in millions per cu. mm. of the plasma. The reliability of the method was controlled by using a special counting chamber for chylomicron estimation.

The mice, which were kept on a sufficient and balanced stock diet, were fasted about 12 hours before each experiment. The animals were divided into 3 subgroups: 1) the non-protein diet group, in which carbohydrates and water were given *ad libitum* during the experiment, 2) the high protein diet group, in which, in addition, plenty of fat-free egg white was given 2 days before as well as during the actual experiment, and 3) the control groups without parenteral administration of fat.

The tissues at the site of the injection were stained with Sudan III and examined microscopically. Additional investigations were made, using the strongly fluorescent 3:4-benzpyrene dissolved in different injection media, and employing fluorescence microscope technique.

Results. No fat in particulate form (lipomicrons) appeared in the blood

either after a fasting period of 12 hours or in the control groups without injections when the animals were kept on fat free nonprotein or high protein diet for 24 hours.

SUBCUTANEOUS ADMINISTRATION. Fig. 1 presents typical "lipomicrographs" obtained from the examination of the blood of the mice. Only minimal amounts of the introduced plain olive oil were absorbed in the form of particles in animals of the nonprotein diet group. In mice of the high protein diet group, olive oil administration, however, caused a clear lipomicronemia. But after previous emulsification, the absorptivity of olive oil distinctly increased. There were no certain differences between the influence of the two emulsions employed. Moreover, in the last mentioned group the diet seemed to have no certain influence.

In general, the absorption was the more rapid, the more finely dispersed the emulsion. The lipomicronemia lasts at least about 24 hours after a single subcutaneous administration when, in all animals, there still was in the subcutaneous tissue plenty of the injected fat left. Because of the fact that in none of the control animals were fat particles observed, the differences were significant.

Microscopic examination revealed that after administration of plain olive oil, the injected material tended to

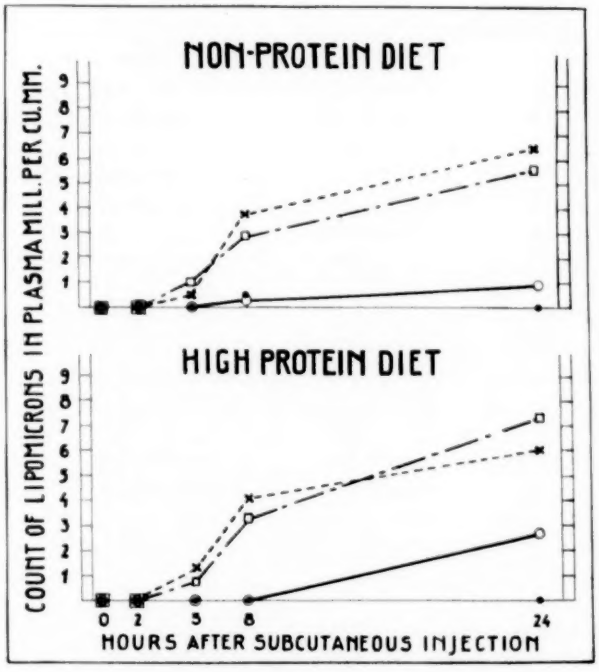

FIG. 1.—Lipomicrographs obtained from the blood of mice after subcutaneous injection of fats.

●———● Control animals without injections
o———o Plain olive oil
x———x Olive oil emulsion with lecithin
□———□ Olive oil emulsion with sodium cholate

form minute droplets at the injection site (the size varying from 3 to 5 microns to larger ones), which fact points to a spontaneous emulsification in the periphery of the fat droplet. It was impossible to establish with certainty whether or not the droplets were located in tissue spaces or in the ordinary lymphatics without any signs of an emulsification. When light petrolatum was injected, the medium was located as larger oily globules in the subcutaneous structures. In the sites of the injections no local lesions could be observed instead of the relatively great amounts of fat.

INTRAPERITONEAL ADMINISTRATION. The individual variations were too great to allow the drawing of a typical lipomicrograph. In general, fat was absorbed considerably more rapidly when injected by this route than when injected subcutaneously, and within about 2 hours there were lipomicrons in the blood. In most cases the visible fat particles disappeared from the blood stream during 24 hours. There were no clear differences between the absorption capacity of the emulsified and the nonemulsified fats. Moreover, cow's milk was absorbed in the form of visible lipomicrons from the peritoneal cavity.

Discussion. Because of their insolubility in water, fats require certain preparations before absorption. Theoretically, as in gastrointestinal digestion, fat is absorbed in 2 different ways: 1) enzymatic formation of water-soluble split products, and 2) absorption in the form of finely dispersed particles. Because the functions of the subcutaneous fat depot seem to be a specific activity of the cells[9], the mechanisms operating in fat depots and in fat that has been introduced parenterally can hardly be compared *per se* with each other. To what extent the subcutaneous structures, except the ordinary fat cells, contain lipolytic enzyme has not been accurately investigated. However, it has been shown with certainty that triglycerides, for example, are saponified to a small extent, thus allowing absorption of minute amounts of fats. Further, it is known that some fats can be transported directly into the blood stream as phospholipids and cholesterin esters, formed enzymatically.

As revealed in the present work, previously emulsified fats, parenterally administered, always cause a distinct visible lipomicronemia in mice. It cannot be stated, however, how large an amount is absorbed and transported further in the state of lipomicrons, and how much in other forms. In addition, some facts point to the possibility that there may also occur a spontaneous, though a relatively minute and slow, emulsification. As it is known, because of their special properties, the commonly occuring alkali salts of the natural fatty acids are good emulsifiers. The most important of the other emulsifying agents in the body are phosphatides (lecithin) and the bile constituents.

It is known that alimentary chylomicrons are covered by a film composed of plasma proteins which make the chylomicron emulsion stable[6]. It is most probable that the physico-chemical state of the stabilized lipomicron emulsion in the blood induced by subcutaneous or intraperitoneal injection is the same in principle. According to the observations reported herein, administration of plain olive oil caused a certain lipomicronemia in the high protein diet group. This fact seems to be in agreement with the "absorbefacient effect" of diet rich in proteins reported earlier[7].

It seems presumable that the formed lipomicrons are carried into the blood along the lymphatics, though not by the thoracic duct. There are known to exist direct communications, espe-

cially in the gastrointestinal canal, and apparently in other sites of the body as well. The alimentary chylomicrons in mice disappear about 3 to 5 hours after entering into the blood. The escape of the lipomicrons from the blood apparently follows the same mechanism as that of the chylomicrons, provided that fats are employed which are absorbed in unchanged form from the gastrointestinal tract. The mechanism in the absorption mechanism of the intraperitoneally introduced fat is possibly similar[10].

The total amount absorbed in the form of visible lipomicrons has not, so far, been determined; it seems plausible, however, that the amount may have some significance also from the nutritional point of view.

If unsaponified mineral oil or unemulsified natural fat is used, the absorption of the substance dissolved in the oil essentially depends on its solubility between the tissue fluid and the solvent used[8] and is always relatively slow. On the contrary, if a quicker effect is wanted, or if greater amounts are to be given, emulsions or various lipo-hydrophilic solvents[5] are more useful.

Summary. It was shown that parenterally administered fats, under certain conditions, enter the blood stream in the form of visible small particles, so-called lipomicrons, the physical state of which most probably is similar in principle to that of the alimentary chylomicrons.

A preceding emulsification of the fat is necessary before it is carried further by the blood as visible particles. In addition, there exists evidence indicating that some spontaneous emulsification may occur also in normal conditions.

The possible absorption mechanism, and the significance of this finding, are discussed in brief.

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SERUM AMYLASE RESPONSE TO PANCREATIC STIMULATION AS A TEST OF PANCREATIC DISEASE

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AN adequate, simple test of pancreatic function in the detection of cases of chronic recurrent pancreatitis is highly desirable. When the disease has progressed to the stage of permanent disturbances of pancreatic function, the diagnosis is evident from the resulting diabetes, steatorrhea, and creatorrhea. Evidence of increased activity of the pancreatic enzymes during an acute exacerbation of chronic recurrent pancreatitis frequently establishes the diagnosis.

An intensive study of pancreatic disease was undertaken at this hospital and our main interest was in the clinical entity of chronic recurrent pancreatitis. As these cases were systematically studied, the diagnosis was readily apparent in those with permanent sequelae or in those cases in which increased serum amylase activity was detected during an acute exacerbation of the disease process[11]. In those cases which had not progressed to the stage of permanent sequelae and were free of acute painful seizures, the diagnosis proved difficult to establish. Studies were undertaken to evaluate the serum amylase response to stimulation of the pancreas in cases of chronic recurrent pancreatitis.

Several investigators have produced an elevated serum amylase level in animals following the injection of pilocarpine[1,10], prostigmine[15], and mecholyl[2,6]. Comfort and Osterberg[5], in a comparative study of different pancreatic stimulants in human subjects, observed that both mecholyl chloride and prostigmine methyl sulfate are especially valuable for the study of secretion of pancreatic enzymes. Popper and Necheles[15] suggested that prostigmine stimulation of the pancreas in man could probably be used to reveal functional insufficiency of the gland, especially in diseased states. Knight *et al.*[9] reported their studies on the serum amylase response following prostigmine stimulation in cases of chronic recurrent pancreatitis. The results of this study revealed that prostigmine stimulation produced characteristic elevation of serial serum amylase levels in cases of pancreatic disease.

Studies were undertaken at this hospital in 1949 to evaluate the serum amylase response following stimulation of the pancreas in patients with pancreatic disease. Chemical stimulation of the pancreas was selected as the more physiological method in that secretion of pancreatic enzymes is mainly under vagal control[3]. Prostigmine methyl sulfate, a safe, effective parasympathetic drug capable of stimulating the secretion of pancreatic enzymes, was used in this study. Consideration was given to the use of secretin; however, it was not used because its chief effect appears to be on the secretion of water and bicarbonate by the pancreas[3,4,8], probably from the cells of the intralobular ducts[8]. Secretin apparently has no direct stimulating effect on enzyme production in the pancreas as observed by Wang, Grossman, and

Ivy[16]. Ten normal patients with no evidence of pancreatic or cholecystic disease as determined by clinical, laboratory, and roentgenological examinations were used as controls. All 10 patients had normal fasting serum amylase values on several determinations prior to administration of prostigmine. Twenty-one cases of chronic recurrent pancreatitis and 4 cases of carcinoma were used to evaluate the response of serum amylase to prostigmine stimulation. The diagnosis in these cases was established by clinical findings and laboratory and roentgenological studies. Increased serum amylase activity during an acute exacerbation was the usual criterion and in some of these cases surgical or postmortem findings confirmed the clinical diagnosis.

Methods. The patient was instructed to fast from midnight until the test was completed. At 8:00 a.m. a fasting serum amylase specimen was obtained. The patient was then given 1.0 mg. of prostigmine methyl sulfate intramuscularly. Specimens for serum amylase values were obtained every ½ hour for 2 hours. The amylase values were determined by the method of Myers[13].

Results. CONTROLS. In the 10 controls, the serial serum amylase values showed little to moderate variation, but in all the amylase values were within the normal range for the method used in their determination (Table 1). The maximum variation in this control series was 118 mg. per 100 cc., which is admittedly high if this value is compared with that obtained by Knight[9]. However, it is conceivable that amylase activity will have a moderate range of variation because of its indirect role in carbohydrate metabolism and regulation of blood sugar, as has been observed and investigated by the author[12], and as has been reported by others[7,13]. Thus it appears that a moderate variation could be expected, but the serial serum amylase values should be within the accepted range of normal (normal range in our laboratory has been found to be 70 to 240 mg. per 100 cc.). The average values of this group are well

TABLE 1.—SERUM AMYLASE VALUES IN CONTROLS BEFORE AND AFTER ADMINISTRATION OF PROSTIGMINE

Name	*Fasting*	*30'*	*60'*	*90'*	*120'*	*Maximum Variation*
M. S.	194	127	94	83	125	−111
N. C.	114	157	142	144	189	75
F. B.	246	249	207	216	187	52
C. L.	130	121	119	157	68	89
E. D.	109	104	59	75	75	−50
P. G.	128	97	79	112	112	−59
W. F.	173	145	222	208	204	77
C. F.	182	136	64	72	114	−118
C. R.	103	110	106	—	115	12
O. B.	140	147	157	93	93	64
Average (10 cases)	152	139	125	129	128	−27

within this range and show an average maximum variation of 27 mg. per 100 cc.

STUDY OF CASES WITH CHRONIC RECURRENT PANCREATITIS. The serum amylase response following prostigmine stimulation in 21 cases of chronic recurrent pancreatitis was studied. The serum amylase values were positive in 17 of the patients, and when plotted, these values gave 3 types of curves, each significantly different from that obtained in the controls. Each case fell into 1 of 3 groups.

Group 1. There were 8 cases in this group and all had an elevated fasting serum amylase value. Following prostigmine stimulation, there was a progressive fall in the serial serum amylase levels, with a slight rise usually in the 90-minute value; the reason for this was not apparent (Table 2). The type of curve obtained in these cases was indicative of chronic pancreatitis without obstruction and was considered diagnostic because of elevated serum amylase values with a progressive fall.

TABLE 2.—SERUM AMYLASE VALUES AFTER PROSTIGMINE STIMULATION IN 8 CASES OF CHRONIC PANCREATITIS WITHOUT OBSTRUCTION

Name	*Random*	*Fasting*	*30′*	*60′*	*90′*	*120′*	*Maximum Variations*	*Comments*
M. C.	328	339	342	308	331	298	44	—
O. H.	491	505	464	361	412	379	134	Confirmed at surgery
M. Z.	436	552	494	492	496	455	97	Pancreatic calculi, hyperglycemia & ch. cholecystitis
P. B.	324	371	216	334	337	333	155	Confirmed at surgery
E. J.	—	333	225	262	251	287	108	Ch. cholecystitis & cholelithiasis
M. C.	676	458	316	351	310	356	148	—
J. K.	308	405	405	348	408	413	65	Confirmed at surgery
F. V.	—	400	360	230	400	120	280	Pancreatic calculi, hyperglycemia, chr. cholecystitis & cholelithiasis
Average (8 cases)		420	353	336	368	330	90	

TABLE 3.—SERUM AMYLASE VALUES AFTER PROSTIGMINE STIMULATION IN 5 CASES OF CHRONIC PANCREATITIS WITH TEMPORARY OBSTRUCTION

Name	*Random*	*Fasting*	*30′*	*60′*	*90′*	*120′*	*Max. Var.*	*Comments*
F. H.	472	794	602	777	750	756	192	Also diabetes
B. O.	869	303	274	526	274	122	404	Chr. pancreatitis at surgery
M. N.	—	460	420	660	540	500	240	Chr. cholecystitis & cholelithiasis
W. S.	297	286	233	256	287	193	94	Previous cholecystectomy
F. S.	305	277	357	355	375	321	98	Also diabetes
Average (5 cases)		414	377	515	445	378	138	

The average maximum variation was 90 mg. per 100 cc.

Group 2. There were 5 cases in this group and all revealed a curve that was characterized by a moderate rise in the serum amylase values, followed by a fall (Table 3). In all but 1 case, the fasting values were above normal, and following prostigmine stimulation, a significant rise in serum amylase values above the fasting value occurred.

The average curve of these 5 patients was indicative of a temporary ductal obstruction, which finally was overcome as the pressure increased and allowed drainage to occur, as reflected in the progressive fall of serum amylase values to a level below that of the fast-

TABLE 4.—SERUM AMYLASE VALUES AFTER PROSTIGMINE STIMULATION IN 4 CASES OF CHRONIC PANCREATITIS WITH OBSTRUCTION

Name	*Random*	*Fasting*	*30′*	*60′*	*90′*	*120′*	*Max. Var.*	*Comments*
S. Q.	478	333	349	494	748	807	474	Confirmed at surgery
V. R.	566	677	683	792	932	976	299	—
W. B.	—	319	396	361	369	462	143	—
J. B.	—	212	230	240	—	598	386	Penetrating duodenal ulcer into head of pancreas with pancreatitis
Average (4 cases)		385	415	472	683	711	326	

TABLE 5.—RESULTS AFTER PROSTIGMINE STIMULATION IN 4 CASES OF CHRONIC PANCREATITIS WITHOUT AMYLASE RESPONSE

Name	*Random*	*Fasting*	*30′*	*60′*	*90′*	*120′*	*Max. Var.*	*Comments*
B. L.	2240 (6–7–50) 257 (6–19–50)							Chr. pancreatitis & cholecystitis with cholelithiasis was confirmed at surgery
	(6–20–50)	149	83	—	197	218	135	
L. S.	349 (6–24–50)							Jaundiced, severe rec. epigastric pain. Nonfunctioning gallbladder with no evidence of stones. No hepatic disease
	(6–28–50)	157	151	175	130	174	45	
H. R.		63	156	175	198	186	135	Cholecystotomy for calculi in 1947. Diabetic type of glucose tol. curve in 1950. Marked calcif. of pancreas on Roentgen-ray exam.
L. G.	481 (11–14–49) 192 (12–16–49) 240 (1–2–50) 234 (1–27–50)							Recurrent severe epigastric pain with abdominal distention. Non-functioning gallbladder with large calculus. Upper G. I. series neg.
	(1–30–50)	166	130	182	156	244	114	

ing one. The average maximum variation was 138 mg. per 100 cc.

Group 3. In this group there were 4 cases of chronic pancreatitis with obstruction and all 4 showed a characteristic rise in serum amylase values following prostigmine stimulation. The rise in serum amylase was progressive, with the 120-minute value much greater than the fasting one. The average maximum variation was 326 mg. per 100 cc. The response obtained in this group was indicative of persistent intrapancreatic obstruction.

Group 4. Out of a total of 21 cases of chronic pancreatitis studied in this series, 4 fall into this group. These cases revealed an elevated serum amylase value during the acute or subacute phase of their painful exacerbations, but all had "negative" prostigmine tests (serial serum amylase values were within normal range) (Table 5).

The diagnosis was clinically established in all 4 cases and confirmed at surgery in 1 patient (B.L.). The only conclusion to be drawn from the "negative" response to prostigmine stimulation is that apparently the pancreatic inflammatory process had completely subsided, and that neither intrapancreatic nor ductal obstruction existed.

Study of Cases with Pancreatic or Common Duct Carcinoma. Studies on the serum amylase response following prostigmine stimulation were undertaken in 4 patients with obstructive jaundice and clinical findings strongly suggestive of malignancy. The amylase response varied so that there was observed no typical curve representative of these cases. The significant feature of the serum amylase response which proved to be diagnostic from a clinical point was the marked rise following prostigmine stimulation. The clinical diagnosis in these cases was confirmed by surgical and postmortem findings.

Discussion and Summary. The need for an adequate and simple test of pancreatic function in the detection of pancreatic disease has been voiced by many. Investigations were undertaken to study the serum amylase response following stimulation of the pancreas in cases of pancreatic disease with early or mild pancreatic dysfunction as reflected solely by an elevated amylase value. Chemical stimulation was selected as the preferable method because of the fact that secretion of pancreatic enzymes is under vagal control. Prostigmine methyl sulfate was used in this investigation and readily produced a significant serum amylase response in cases with pancreatic disease. The encouraging results reported by Knight *et al.*[9] proved invaluable in interpreting and evaluating the various amylase values obtained in this study.

The 10 controls used in studying the serum amylase response to prostigmine stimulation revealed a moderate variation in values, but all were within the accepted range of normal (70 to 240 mg. per 100 cc.). The average curve in this group sloped downward slightly with an average maximum variation of 27 mg. per 100 cc.

Twenty-one cases of chronic pancreatitis were studied following prostigmine stimulation. Significantly elevated serum amylase values were evident in 17 of these cases (81%), while 4 cases had a "negative" prostigmine test (19%). The serum amylase values in the "positive" prostigmine test cases, when plotted, gave 3 different types of curves, each significantly different than that obtained in the control group. The curves were of clinical significance in that they usually revealed the presence of pancreatic cellular inflammation with or without intrapancreatic or ductal obstruction. The curves also indicated the degree of obstruction present. Four cases of chronic recurrent pancreatitis failed to reveal an abnormal serum

amylase response following prostigmine stimulation. The basis for the "negative" test in these 4 cases is not clear, but it appears that the acute pancreatic inflammation had entirely subsided when the prostigmine test was performed.

Four cases of pancreatic or common duct malignancy were also studied. All 4 cases had significant curves that revealed marked elevation of serum amylase values, which proved to be diagnostic. The curves obtained in this group did not have a characteristic pattern.

Conclusions. Prostigmine stimulation of the pancreas has a value in the study of patients suspected of having pancreatic disease.

The test may be of value in cases seen shortly after an acute episode suspected of being chronic recurrent pancreatitis, especially when clinical symptoms have subsided. A significant elevation of serum amylase values above normal following prostigmine stimulation is diagnostic.

The prostigmine test is a fairly adequate, simple test that has been diagnostic in 81% of the cases studied here. The test is limited in that it is only a simple clinical evaluation of pancreatic function and is not to be compared to the more informative tests of pancreatic physiology and enzyme concentration as determined by duodenal intubation and hormonal stimulation.

The simplicity of the prostigmine test adds to its usefulness and it can be readily performed in any hospital or office equipped to make serum amylase determinations.

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TYPHOID FEVER: CHLORAMPHENICOL THERAPY AND THE PROBLEM OF RELAPSE

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The amelioration of symptoms of typhoid fever by chloramphenicol is no longer seriously disputed, for the beneficial effects of the drug, as initially reported[16], have been confirmed by many independent investigators[4,8,11,12]. However, the voluminous literature on this subject contains an increasing number of reports of relapses of chloramphenicol-treated typhoid fever and persistence of positive stool cultures during and after therapy. The presence of S. *typhosa* in the stools of individuals who are afebrile and clinically improved tends to favor the release of infected persons into the general population. This clinical improvement without cure makes chloramphenicol therapy of typhoid fever considerably more complex than it appeared when this valuable agent was introduced. It is the purpose of this paper to present 3 cases of typhoid fever that illustrate some of the problems arising in association with chloramphenicol therapy.

Case Reports. Case No. 1. Three weeks prior to admission, S.S., a 14-year old colored girl, was visiting in another state and became ill. She presented symptoms of chills, fever, and diarrhea and the condition was diagnosed as typhoid fever. Seven days after the onset, therapy was started with chloramphenicol; 3 gm. of the drug were given initially and 0.75 gm. daily thereafter for 9 days. Her temperature returned to normal within 6 days after treatment was instituted and she was allowed to return home after being afebrile for 4 days.

When admitted to this hospital on Sept. 21, 1949, at the request of the public health authorities, her temperature was normal and her physical examination negative. The patient's temperature rose to 102° F. on the 3rd hospital day and a stool culture obtained at this time was positive for S. *typhosa* (Chart 1). Chloramphenicol therapy was started on the 8th hospital day and was continued for 5 days for a total of 10 gm. Cultures became negative and the temperature was normal within 4 days after the onset of therapy. Treatment was cut short purposely on this occasion to determine whether the prompt remission was due to the antibiotic or to the natural evolution of the disease.

On the 26th hospital day (51st day of the disease), blood and stool cultures obtained from the patient were positive for S. *typhosa* and again her temperature rose to 102° F. Another course of chloramphenicol was started and a total of 25 gm. was given over a period of 12 days. She became afebrile on the 3rd day of therapy and cultures were negative. There was no relapse during the 3-week follow-up period.

The infecting strain of S. *typhosa* was sensitive *in vitro* to 5 γ of chloramphenicol per cc. The patient was on a 6-hour dosage schedule and antibiotic plasma determinations were performed periodically during treatment. The levels were found to range from 20 to 30 γ of chloramphenicol per cc. after a 1-gm.

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dose, and from 10 to 15 γ per cc. after a 0.5-gm. dose.

COMMENT. The first 2 courses of chloramphenicol therapy, one prior to admission to the hospital and the initial course given in the hospital, were inadequate when compared to dosage schedules currently recommended[12]. One course of treatment was cut short purposely to determine whether the prompt control of fever and symptoms was really assignable to the antibiotic. The patient relapsed within 14 days after a 5-gm. total dose was administered over 4 days, whereas she relapsed within 10 days after a total dose of 10 gm. over a 7-day period. Thus a longer remission was actually obtained with the smaller total amount of drug the second time it was administered. This lack of correlation of relapse time to duration of therapy has been noted by other investigators[10]. It is suggested that in this patient chloramphenicol had a suppressive rather than a curative effect. This may be a reflection of the *in vitro* bacteriostatic nature of the drug; it has been reported that as much as 1000 γ of chloramphenicol per cc. fail to kill the typhoid bacillus[15].

The 2 relapses and the protracted course of illness suggest that inadequate therapy may suppress the symptoms and prolong the disease. The lack of correlation between symptomatic and bacteriologic control of typhoid fever emphasizes the necessity of strict observance of public health regulations prior to the release of a patient from an institution after chloramphenicol therapy. Had it not been for alert public health officers, the above patient might have become a focus of a typhoid fever outbreak.

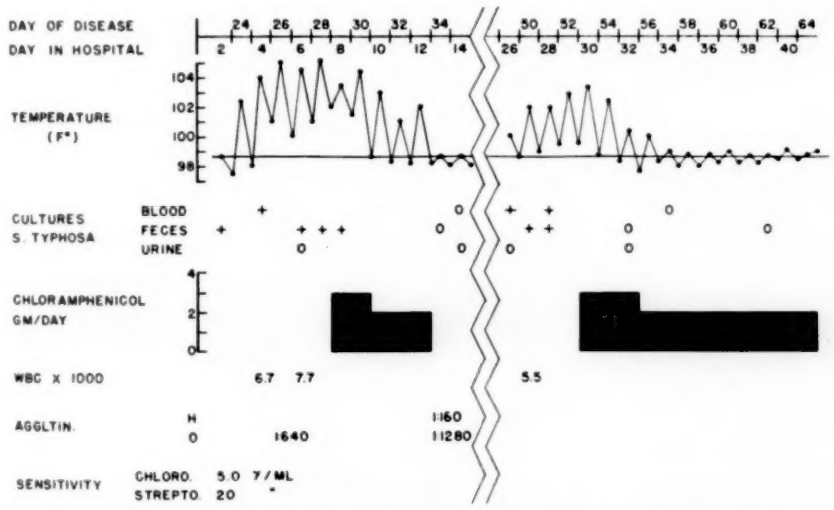

CHART 1.—Clinical course in Case 1 (Patient S.S., 14 years old, weight 80 lb.).

CASE NO. 2. M. C., a 20-year old colored woman, was admitted to the hospital on Dec. 4, 1949, with the chief complaints of headache, chills, and diarrhea. Her illness began 9 days prior to admission at which time she had a high fever and frequent chills. The symptoms were severe enough to confine her to bed. The patient was treated by her physician with penicillin and sulfonamide drugs with no beneficial results. She had diarrhea for 3 days before coming to the hospital.

Physical examination revealed a malnourished, acutely ill woman in a semi-comatose state, temperature 104° F. and pulse

100. No other abnormal findings were noted.

S. typhosa was recovered from the blood culture taken on admission (Chart 2). Inasmuch as the organism was sensitive to 1 γ of aureomycin per cc. *in vitro*, it was decided that the intravenous form of this drug be given a trial. Therapy was discontinued after 3 days when the patient did not respond either clinically or bacteriologically. Chloramphenicol was started on the 6th hospital day, the patient receiving 3 gm. daily for 7 days and then 2 gm. daily for 5 days for a total of 31 gm. She showed clinical improvement within 24 hours, and her temperature was normal on the 4th day of this treatment.

The patient's chloramphenicol plasma concentrations after a 0.5 gm. dose of the drug ranged from 7.5 to 30 γ per cc. over a 6-hour period. The infecting organism was sensitive *in vitro* to 12 γ of chloramphenicol per cc.

COMMENT. This patient illustrates a good symptomatic and bacteriologic response to chloramphenicol in the initial phase of her disease. Despite the adequate treatment of 31 gm. of chloramphenicol over a period of 12 days, she relapsed 10 days after the

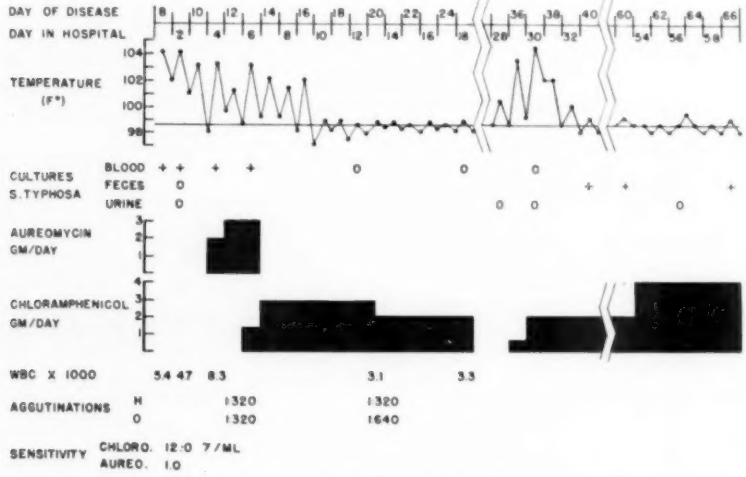

CHART 2.—Clinical course in Case 2 (Patient M.C., 20 years old, weight 100 lb.).

She was afebrile and cultures were negative until the 29th hospital day (35th day of the disease), at which time the temperature rose to 104° F. Blood culture was negative but S. *typhosa* was recovered from the stool. Chloramphenicol, 2 gm. daily, was again started, and the temperature returned to normal within 3 days. The stools, however, continued to be positive for S. *typhosa* despite 30 successive days of treatment with 71 gm. of chloramphenicol. On her 62nd hospital day, aureomycin, 2 gm. daily, was substituted for the chloramphenicol. Stool cultures became negative after 8 days of aureomycin therapy and remained free of S. *typhosa* for the duration of treatment (29 days). The patient was observed for 3 weeks after therapy was discontinued and was discharged as cured.

drug was discontinued. The second course of the antibiotic, though effective in causing defervescence, failed to render the stools negative for S. *typhosa*. The transient carrier state persisted during therapy with 71 gm. of chloramphenicol over a 30-day period. The lack of effect of the drug in the "tissue" phase of the disease has been observed by other investigators[3,5,6,8,14]. It is suggested that this patient's disease passed from a controlled to an uncontrollable state by the discontinuance of specific treatment. The possibility of this occurrence

should make one hesitate to employ "block" therapy in typhoid fever.

Aureomycin did not appear to be effective in the initial stage of the disease though the adequacy of the trial in this case is questionable. The employment of aureomycin in the "tissue" phase of the disease may have been a factor in producing the ultimate negativity of the stools, but this is mere speculation.

An initial diagnosis of meningitis was ruled out by performing a lumbar puncture and studying the spinal fluid. The leukocytes numbered 4,300 per cu. mm., blood culture was negative, and the typhoid agglutinations were not diagnostic of the disease (Chart 3). At first the patient's temperature declined slowly with no specific therapy. On the 15th hospital day (18th day of disease) the temperature rose to 105° F. and a blood culture was reported as positive for S. *typhosa*. Chloramphenicol was started on the 23rd hospital day, the patient receiving 3 gm. daily

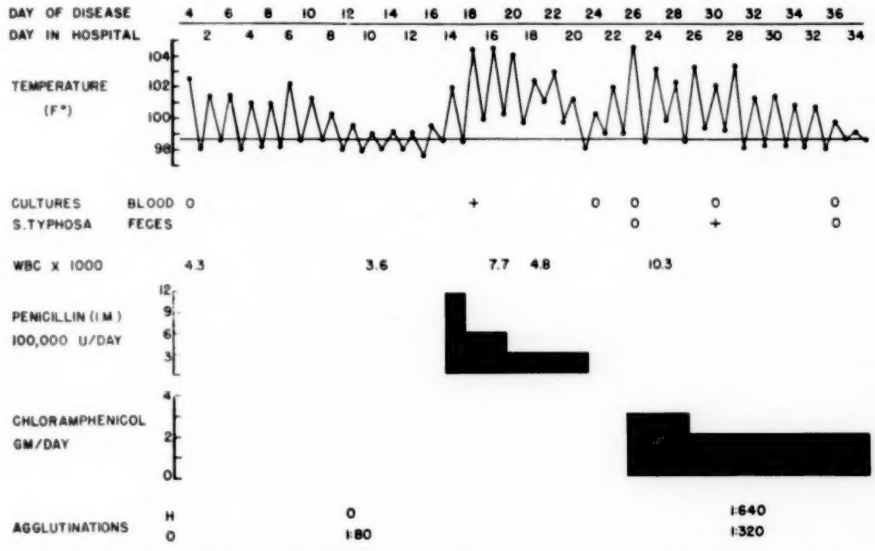

CHART 3.—Clinical course in Case 3 (Patient L.J., 20 years old, 4 months pregnant).

CASE No. 3. L. J., a 20-year old colored woman, was admitted to the hospital with a history of headache and stiff neck of 3 days' duration. The patient was well until 3 days prior to admission, at which time she began having severe frontal headaches which were not relieved by aspirin. She also noted at this time difficulty in bending and rotating her head. A visiting nurse discovered that the patient was febrile and recommended hospitalization. She was 4 months pregnant.

Physical examination revealed a well developed and well nourished pregnant woman. She appeared in no acute distress but was somewhat lethargic. Temperature on admission was 102.4° F., pulse 108. The uterus was found to be enlarged to the extent of a 4-months' pregnancy. There was moderate nuchal rigidity.

for 3 days and then 2 gm. daily until a total of 36 gm. was given. The duration of therapy was 16 days. A stool culture was positive for S. *typhosa* on the 4th day of treatment and the temperature did not become normal until the 10th day. The patient remained afebrile and the stool cultures were negative for a 3-week follow-up period after the discontinuance of therapy.

The organism in this case was inhibited *in vitro* by 12.5 γ of chloramphenicol per cc. Two antibiotic plasma determinations at ½ and 6 hours after one of the doses were found to be 7.5 and 5 γ of chloramphenicol per cc., respectively.

The patient was subsequently readmitted to the hospital at term and she had a normal uncomplicated delivery.

COMMENT. This patient's symptomatic response to chloramphenicol was not considered to be a good one because of the delayed defervescence. The failure to respond well may have been a reflection of the low antibiotic concentrations achieved in her blood on the basis of the doses given.

Pregnancy and typhoid fever do not commonly occur in combination (1 to 3%) but when the two conditions coexist, abortion or premature labor results in approximately 40 to 60% of the cases[13]. Chloramphenicol may have obviated the complication in this case.

Discussion. Patients 1 and 2 illustrate that beneficial symptomatic effects may be observed when chloramphenicol is employed in the treatment of typhoid fever. A sense of general well-being usually precedes the defervescence that is commonly noted within 4 days after the administration of adequate therapy. The third patient was given 36 gm. of chloramphenicol over a period of 16 days and yet the response was not a striking one. Plasma concentrations were low in this individual indicating either a poor absorption or a rapid inactivation of the antibiotic by the body.

The phenomenon of relapse in typhoid fever after chloramphenicol therapy has yet adequately to be explained. In the era of nonspecific therapy of typhoid fever relapses occurred in approximately 3 to 16% of the cases[13]; this rate of relapses seems to be little altered[4,8,11] or even higher in some reports[10] when specific therapy is employed. It is a real question whether the term "relapse" has the same connotation in the older literature and in the more recent years when specific therapy has been available. Admittedly typhoid fever is a variable disease, but in the older reports relapses were said to occur when there was a recrudescence of fever and symptoms after the initial infection had run a course over periods as long as 42 days. In the discussions of antibiotic therapy of typhoid fever, "relapses" occured within 10 to 16 days after a course of treatment had supposedly controlled the infection. Thus several "relapses" under the more recent definition may occur during the interval formerly regarded as necessary for the initial infection to run its course (28 to 42 days with extremes as high as 70 to 90 days).

This leads to interesting speculation as to the nature of typhoid infections and the action of chloramphenicol in this disease. Although typhoid fever is a bacterial disease and an "intracellular or tissue" phase in its evolution has not been emphasized as it has in brucellosis or malaria, nevertheless, the harboring of typhoid infection in the asymptomatic form is recognized, that is, carrier state, chronic osteomyelitis, and it has been reported that *S. typhosa* can be demonstrated in the young plasma cells in the tissues of the patients[1,9]. In the early and invasive phase of typhoid fever, chloramphenicol may have its greatest usefulness, but once the disease has become established, the drug may merely control symptoms and not alter the basic recovery pattern of the patient to any great degree. The latter fact is evident by the occasional persistence of positive stools during therapy[3,8,14,16] and the failure of the antibiotic in the treatment of the carrier state[3,5,14]. The question even arises as to whether specific therapy in the form of chloramphenicol interferes with the natural evolution of antibodies. Some cognizance of this possibility has been taken by the French workers who, at the same time that chloramphenicol therapy is started, subject their typhoid patients to treatment with convalescent globulins and serum obtained from hyperimmunized animals[2].

Chloramphenicol is a bacteriostatic

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agent. When suppression therapy is employed it is essential that the suppressive agent be used for a sufficiently long time. This may be accomplished by a) "block" treatment or b) continuous therapy. Under either circumstance, however, the total duration of therapy should probably coincide with the accepted "average" duration of unmodified typhoid fever. With the discontinuous type of therapy, the patient is treated initially until he is asymptomatic and then, after a short rest period, treatment is again begun at a time calculated to correspond with the incubation period of the organism. This program is bacteriologically sound and is based on generation time and recovery time of the organisms subjected to growth suppression by chloramphenicol. However, the wisdom of allowing an organism as virulent as the typhoid bacillus to regain even a little of its vitality is questionable. The difficulty encountered in the treatment of carriers plus the fact that the carrier state has occurred after chloramphenicol therapy[5] makes one hesitate to employ any therapeutic program that might be interpreted as "minimal". It is agreed that prolonged continuous therapy will be in excess of the needs of many typhoid patients, but this is justifiable when one considers the epidemiological importance of the disease.

Summary. Three patients with typhoid fever were treated with chloramphenicol. These cases illustrate problems which occasionally arise even when this specific antibiotic is employed in the treatment of the disease, that is, relapses, persistence of positive stools during therapy, and delayed defervescence. A discussion is presented in an effort to explain these undesirable effects. The evidence seems to indicate that chloramphenicol therapy of typhoid fever is suppressive rather than curative. It is suggested, therefore, that the total duration of treatment should probably coincide with the accepted "average" duration of unmodified typhoid fever if the best results are to be obtained.

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EXTREMITY BLOOD FLOW IN THE DOG IN THE PRESENCE OF OBSTRUCTIVE ARTERIAL CLOTS*

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IN recent years much has been written concerning the role of reflex vasospasm caused by an obstructed arterial segment[10-14]. The obstruction may be caused by an area of thrombosis, a recent or old embolus, a scar, or an aneurysmal sac which was left in place at operation. These obstructed areas along an artery are believed to act as irritating foci which give rise to vasoconstrictor impulses, via the sympathetic nerves, resulting in spasm of the collateral vessels around the lesion.

Consequently, it has been advocated that resection of the obliterated segment of artery will eliminate the irritating focus, allow the collaterals to dilate, and thereby increase the circulation to the part. Leriche has been the outstanding proponent of this hypothesis[12-14]. Although he and his associates have done much experimental vascular work on dogs, most of the evidence supporting this theory has been obtained by clinical observation of the subjective and objective improvement of the patient (for example, return of skin temperature and color to nearly normal, and increase in the arterial pulse volume of an extremity) following resection of a segment of artery.

The authors therefore planned to study the problem by measuring the actual extremity blood flow, by means of the venous occlusion plethysmograph, before and after production of obstructive arterial lesions, and subsequently after resection of the lesion.

Experimental Method. Healthy mongrel dogs weighing 9 to 20 Kg. were used in all experiments. Pentobarbital sodium (nembutal) anesthetic, 64 mg. per 5 pounds of body weight, was used, and aseptic technique was carried out in all operations.

It was necessary to develop a method by which an obstructive clot could be consistently produced within an arterial lumen. Several traumatic and irritating procedures used by other workers[8,9,15,17,19] were tried but the results were found to be inconsistent and unreliable. Clots formed by the injection of thrombin or other coagulating agents into an isolated arterial segment containing blood were soft and would move down the vessel wall and disintegrate. A modification of the method used by Dees and associates[2,4,16] in extracting renal stones was finally developed. Briefly, the technique was as follows:

An arterial segment, usually 2 to 4 cm. in length, was isolated between bulldog clamps. (This segment of artery was observed to go into spasm consistently during the operative manipulation.) A No. 25 gauge needle was introduced; the blood was withdrawn into a tuberculin syringe and its volume measured. Leaving the needle in place, the syringe was detached and another containing either 70% alcohol or sodium mor-

* This investigation was supported in part by a research grant from the Medical Research and Development Board, Office of The Surgeon General, U. S. Army.

rhuate was attached. A volume of this material equal to the volume of blood aspirated was injected and allowed to remain 5 or 10 minutes. At the end of this time the solution was withdrawn and the lumen flushed several times with physiologic saline solution.

This initial step of irritating the intima was believed to be necessary to make the clots "stick" in a straight artery. Apparently the irritation increases the microscopic permeability of the intima and thus allows the coagulum to become more securely attached.

Thrombin solution, 0.02 to 0.05 cc. (100 units per cc.), was injected into the artery and followed by a volume of fibrinogen solution* (0.04 gm. of fraction 1 per cc.) 1.5 times greater than the volume of blood originally aspirated. This slightly distended the artery and was a necessary step in making the clot remain in place after release of the clamps, because of spasm of the vessel following operative trauma. Five minutes after the injection of fibrinogen, the needle could be withdrawn without leakage.

Five minutes after removal of the needle, the proximal bulldog clamp was released and the clot allowed to pack against the distal clamp for an additional 5 minutes. If a satisfactory clot formed, it would remain clear and not become blood stained subsequent to removal of the proximal clamp. If blood flowed around the coagulum, the clamp had to be reapplied and a small amount of thrombin introduced into the lumen at the proximal end of the thrombus. Again, a period of 10 minutes was allowed to pass before the clamps were released in the order previously described. The wound was closed in layers with interrupted cotton sutures.

While the technique was being developed, many clots were excised at various intervals from 24 hours to 4 months postoperatively for gross and microscopic examination. They were thus studied in progressive stages of organization. When the arteries were divided just distal to the clots, the proximal ends would not bleed, showing that the clots did not permit the passage of blood through or around them. A specimen is shown in Fig. 1. Fig. 2 shows an arteriogram made 1 month after a clot was formed in the femoral artery.

The blood flow in the hind limbs of the dogs was measured with an optically-recording, venous occlusion air plethysmograph similar to the one described by Eckstein and others[6]. Flows were measured with the animals under pentobarbital sodium (nembutal) anesthesia, lying on one side with the extremity elevated slightly above body level to insure good venous drainage.

The entire lower portion of the hind limb, from the knee downward, was sealed in the plethysmographic boot. Thus, while limb volumes varied from dog to dog, the same relative portion of the extremity was used in all.

Room temperature was kept as nearly constant as possible during each experiment by means of air conditioning, and it usually did not vary more than 2° to 3° in the range of 72° to 80° F. Blood pressure measurements were taken between flow measurements with the tail plethysmograph described by Deterling and Essex[5].

Experiment 1. The femoral artery just below the inguinal ligament was selected as the site for producing the clots. Five animals were used. At the beginning of the experiment, 2 or 3 preoperative blood flows were taken on each animal, usually 4 to 7 days apart, in order to establish a basal level. Postoperative measurements were taken immediately after operation, 24 hours after, and every other day thereafter until the flow reached a preoperative value (Table 1A).

It can be seen that there is a rather wide range of normal flow in each dog as well as in the group. Most of the

* Detailed information on the reactions of thrombin and fibrinogen, and the physical properties of the resulting coagula, is presented in the excellent monographs of Ferry and Morrison[7], and Dees and associates[3,4,16]. It was found that 1 unit of thrombin will clot 1 cc. of fibrinogen (fraction 1) solution in a test tube of 1 cm. inside diameter, in approximately 45 seconds if the fibrinogen concentration is 10 gm. per liter, pH approximately 6.3, ionic strength 0.15, and the temperature 25° C.

It is to be emphasized that in producing clots by this method only fresh solutions of thrombin and fibrinogen should be used. Solutions in the concentration described can be refrigerated and used for 3 days after being made, but after longer periods of storage they may produce soft clots which tend to fragment easily.

E. R. Squibb and Sons kindly furnished the fraction 1 of human plasma used in this study.

animals developed a rich bed of collaterals which supplied, within 24 hours after the femoral artery was clotted, a total blood flow equal to that before operation. In this group, plethysmography was performed on the 3rd and 5th postoperative days to determine whether there was any diminution in flow. There was no decrease in flow in any of the 5 animals; in fact, there was a slight increase in 2 of them.

Experiment 2. Since blood flow returned to normal so rapidly after the formation of clots in the femoral artery in Experiment 1, it was decided to repeat the same experiment after ligating the main vessels which supply collateral circulation to the hind limb.

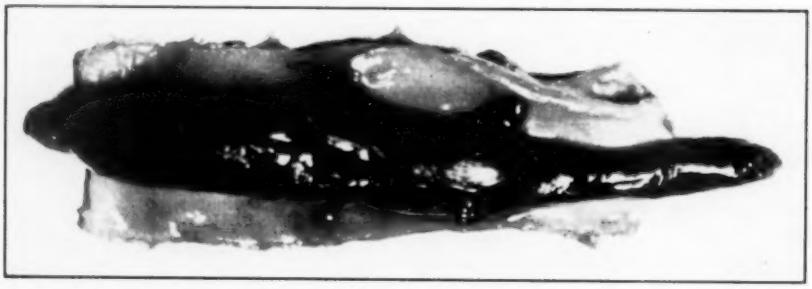

FIG. 1.—A clot in an arterial segment 24 hours after production.

FIG. 2.—A diodrast arteriogram made one month after a clot was produced in the femoral artery.

TABLE 1.—EXTREMITY BLOOD FLOW IN DOGS IN THE PRESENCE OF OBSTRUCTIVE ARTERIAL CLOTS*

Dog No.	Sex	Weight (lb.)	Preoperative Flow (Average) (cc.)	Postoperative Flow			
				Immediate (cc.)	24 Hours (cc.)	3 Days (cc.)	5 Days (cc.)
A. Clot in Femoral Artery							
4	M	20	10.2	†	7.9	14	16.7
5	F	29	9.3	4.8	12.6	16.6	16.2
6**	F	30	14.7	3.1	15	25	†
7	M	22	12.5	4.7	9.5	11.1	10
8	M	32	7.7	1.5	8.7	9	10
B. Clot in Femoral Artery, and Collateral Vessels Ligated							
10	F	30	10	8.2	14.6		
13	F	40	13.9	8.5	13.4		
14	F	27	14.7	7.7	17		
16	M	25	13.2	3.9	5.7		16
C. Clot in Femoral, Popliteal, and Saphenous Arteries, and Collateral Vessels Ligated							
17	F	31	10.8		5		
36	M	28	11.6		10.2		
38L††	M	24	12.5		21		
38R	M	24	11		20		
41	M	30	8.5		16		
44	F	32	10		11		

* All measurements were made by means of the venous occlusion air plethysmograph. Blood flows are expressed as cubic centimeters per 100 cc. of leg tissue per minute.

† No seal was obtained on the plethysmograph.

** Dog No. 6 was kept in the plethysmograph for 8 hours postoperatively, at which time the blood flow had reached 9.4 cc. The dog was removed from the plethysmograph because of a fall in blood pressure due to an overdose of anesthetic.

†† Both hind legs of Dog No. 38 were used, but the experiments were done approximately 1 month apart.

This was carried out on 4 dogs. In each, the abdomen was entered and the deep circumflex iliac artery, which arises from the aorta, the common hypogastric, and the epigastro-pudendal trunk, which gives rise to the deep femoral, were ligated and divided on the right side.

A period of 1 to 2 weeks was allowed for the animals to recover from the operation before pre-clotting blood flows were measured. Clots were produced in the femoral arteries as described in Experiment 1. Postoperative studies were made immediately after the procedure, and 24 hours later (Table 1B). It can be seen that ligation of the collateral vessels before clots were produced in the femoral artery had little effect on the time required for the blood flow to return to normal.

Experiment 3. Because of the unsuccessful attempts in Experiments 1 and 2 to embarrass for an appreciable length of time the blood supply to the dog's hind leg by occluding the femoral artery, it was decided to place the clots in the popliteal artery. Four dogs were prepared by ligating and dividing the deep circumflex iliac, the hypogastric, and the epigastro-pudendal arteries on the right side as described in Experiment 2. After allowing 2 or more weeks for the animals to recover completely from the operation, pre-clotting blood flows were measured. Fibrin clots were then formed in each vessel, 1 to 2 cm. on each side of the bifurcation of the femoral artery into the popliteal and

saphenous arteries, just above the knee. In the process of isolating these vessels for the application of bulldog clamps it was always necessary to ligate several small muscular branches.

Table 1C summarizes blood flow data before and after operation in this group. Again it is obvious that obstructing the main arterial channels to the hind limb, even at the origin of the popliteal artery, reduces the limb blood flow for a period of less than 24 hours and results in no permanent damage.

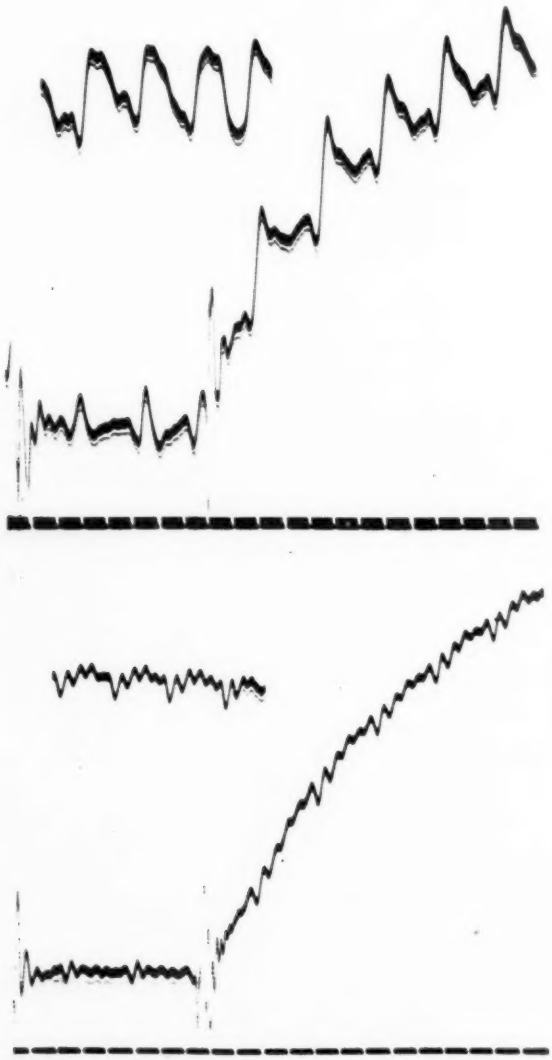

FIG. 3.—*a*, Preoperative plethysmographic blood flow pattern. The short tracing at top left was obtained with the limb resting in the airtight boot. *b*, Blood flow pattern in the same dog 24 hours postoperatively. Note the marked damping of the waves produced by the clot. The total blood flow is greater, however, than the preoperative value.

In only 1 dog of this group, No. 17, was there a temporary reduction in flow postoperatively. Consequently, this animal was studied on the 3rd and 7th postoperative days. The flows on these days were 7.1 and 11.2 cc., respectively.

In 2 animals of this group, the blood flows 24 hours after clotting were considerably above the preoperative values.

Figs. 3a and 3b show the flow patterns of dog No. 41; these patterns are typical in form of all the others. The preoperative wave pattern is characterized by rapid increases in volume in a steplike fashion with each pulse wave. However, after obstruction of the main artery the large waves of the flow curve are practically abolished and the tracing makes a steadier and more uniform rise as the limb fills through collateral channels.

Discussion. In striking contrast to the sequence of reactions in the human limb caused by an embolus or sudden occlusion of the femoral or popliteal artery, the formation of fibrin clot in corresponding portions of the arterial tree in the dog, even after major collateral channels had been ligated, resulted in only a temporary diminution in blood flow to the leg, lasting usually no longer than 24 hours.

There are 2 possible explanations for this phenomenon: (1) In producing the clots in all of the animals used in these experiments, the femoral arteries were mobilized and lifted from the vascular sheaths so that clamps could be applied. In freeing the arteries from the vascular sheaths, it is possible that sensory nerves were interrupted. (2) If the sensory nerves of the clotted segment were not damaged appreciably, and it is felt that they were not, this behavior may mean that reflex vasospasm after an arterial insult in the dog is not of the same order of magnitude as that found in the human subject, and that the potential collateral vessels are comparatively larger, and have larger and more numerous communications than in the human.

Summary and Conclusions. The work reported here was carried out in an effort to study reflex vasospasm caused by obstructed arterial segments. A method for the uniformly-controlled production of intra-arterial clots in the dog is described.

Blood flow measurements in the dog's hind leg before and after obstruction of the femoral or popliteal and saphenous arteries with clots showed that the circulation returned to normal value 24 hours after operation. The measurements were made by means of the venous occlusion air plethysmograph.

Intra-abdominal ligation and division of the main collateral vessels to the hind limb did not affect the blood flow before or after the production of clots in the femoral artery alone, or at the junction of the femoral, saphenous, and popliteal arteries.

The dog was found to be an unsuitable experimental animal for work on this problem using this particular technique.

The authors wish to express their appreciation to Mr. Richmond Waits for valuable technical assistance.

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SOME ASPECTS OF ADRENOCORTICAL FUNCTION IN CARDIAC DECOMPENSATION*

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It has been suggested that the adrenocortical hormones may participate in the production of the edema of cardiac decompensation by reason of their well known effects on mineral and water metabolism[7,9,10,20]. Parrish[20] reported an increase in biologically active glycogenic corticoids in the pooled urine of 10 patients with congestive heart failure but added that a urinary extract of only 4 of them prolonged the survival time of adrenalectomized rats. Deming and Luetscher[7] stated that the urine of similar patients with congestive failure and nephrosis contained a greater amount of sodium-retaining factor than was present in the urine of nonedematous controls.

In a previous communication[13], two of us reported low urinary 11-oxysteroids and 17-ketosteroids in 20 cases of cardiac decompensation. The formaldehydogenic corticoids were determined by the method of Daughaday and Jaffe[5] and the 17-ketosteroids by the method of Holtorff and Koch[11]. These data, together with information subsequently collected in several additional patients, are summarized in Table 1 and diagrammed in Figs. 1, 2, and 3. The cardiac status of the 11 patients selected for further adrenocortical evalution is also listed in this table, being classified as mild (little fluid retention and few symptoms), moderate (considerable water retention and severe symptoms which responded well to bed rest, digitalis, and mercurial diuretics), and severe (similar to moderate, but responding poorly to therapy). F.H., who exhibited severe decompensation of comparatively recent onset, but who was refractory to specific therapy, was studied partially at 4 and 9 months and more completely at 6 and 11 months following onset of symptoms.

Methods and Results. In order to evaluate the ability of the adrenal cortex of these patients to respond to stress, insulin tolerance tests were performed[8] and the 4-hour percentage drop in circulating eosinophils noted[1,22] (Table 1). Increased insulin sensi-

* This study was made possible through the generosity of Schering Corporation.
† Schering Fellow in Endocrinology, 1949-51.

tivity was observed in several patients whose initial onset of congestive failure was longer than 6 months, and most showed hypoglycemic unresponsiveness as evidenced by a prolongation of the period of hypoglycemia with failure of the blood sugar to return to fasting levels by 90 to 120 minutes, as occurs in normals[8,18] (Fig. 4). F.H. exhibited a normal insulin tolerance curve at 6 months (Fig. 4, F.H. 1) but increased insulin sensitivity and hypoglycemic unresponsiveness when the test was repeated at 11 months (Fig. 4, F.H. 2).

In spite of the prolonged lowering of the blood sugar, usually sufficient to give a normal fall of eosinophils, the response of the eosinophils was below normal in 6 of 9 patients, and diminished and normal in 2 tests done at different times in the 10th. (Table 1). The remaining patient had a low fasting count, so that the 4-hour change was unreliable.

Two patients, H.T. and F.H., were

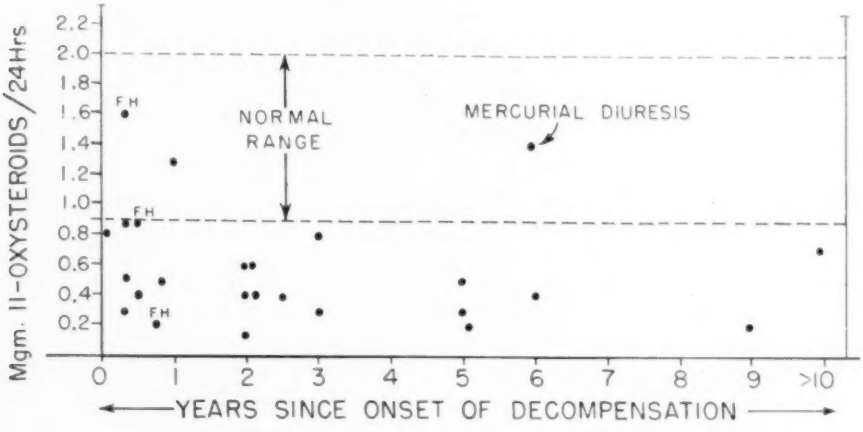
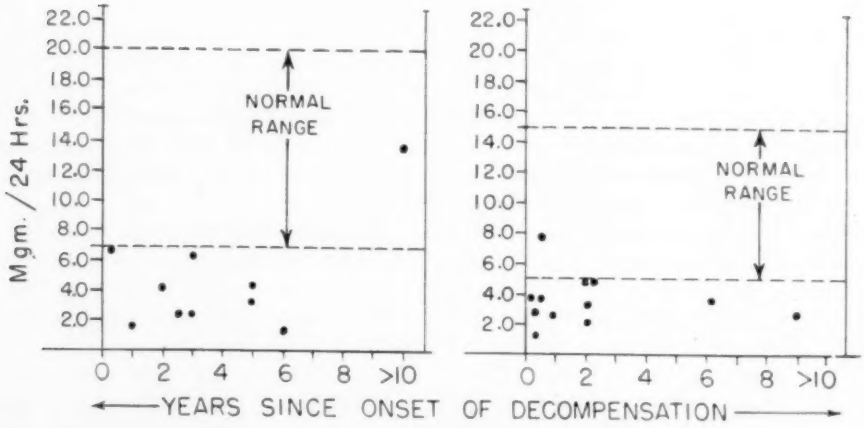


FIG. 1.—Urinary corticoid values in cardiac decompensation.



FIGS. 2 (left) and 3 (right).—Urinary 17-ketosteroids in cardiac decompensation. Fig. 2, males. Fig. 3, females.

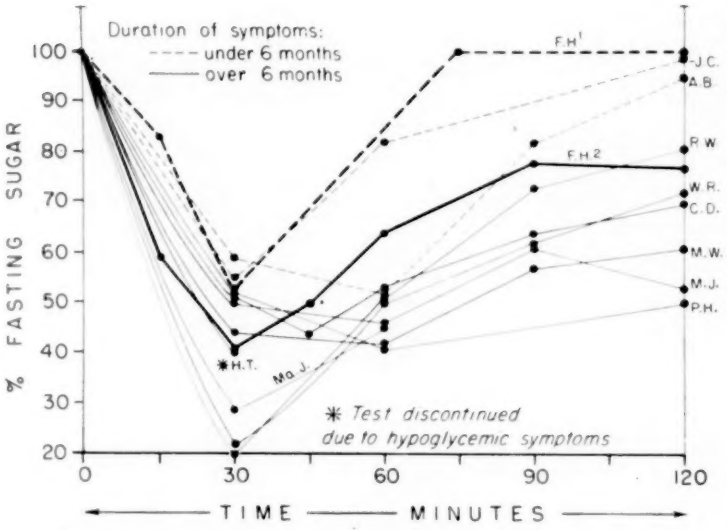


FIG. 4.—Insulin tolerance tests in cardiac decompensation.

TABLE 1.—URINARY 11-OXY- AND 17-KETOSTEROIDS IN 23 PATIENTS IN CARDIAC DECOMPENSATION

Patient	*Age*	*Sex*	*Etiology*	*Duration of Symptoms (in years)*	*Status of Decompensation*	*% fall of Eosino.*	*Urine Volume cc./24 hours*	*11-oxysteroids mg./24 hours*	*17-ketosteroids mg./24 hours*
W. R.	21	M	Rheumatic	10	Mild	38	1640	0.7	13.3
M. W.	44	F	Rheumatic	9	Severe	22	390	0.2	2.8
P. H.	41	M	CCP	6	Severe		2027	1.4*	1.4
C. F.	60	F	ASHD	6			1200	0.5	4.1
J. M.	68	M	HCVD	5			550	0.5	3.4
H. S.	63	M	ASHD	5			620	0.3	4.3
D. L.	21	F	Rheumatic	5			150	0.2	
T. M.	60	M	ASHD	3			590	0.3	2.3
A. C.	54	M	Syphilitic	3			1322	0.8	6.4
D. M.	55	M	ASHD	2-1/2			455	0.4	2.3
W. T.	74	M	ASHD	2			720	0.6	4.1
H. T.	40	F	Congenital	2	Severe	30	920	0.12	3.2
R. W.	45	F	Rheumatic	2	Moderate	37	1055	0.4	5.0
C. D.	64	F	HCVD	2	Moderate	37	600	0.4	2.3
Ma. J.	59	F	ASHD	2	Mild	69	1130	0.6	5.0
D. K.	65	M	ASHD	1			365	1.3	1.6
M. J.	60	F	ASHD	5/6	Mild	59	900	0.5	2.8
J. C.	58	F	ASHD	1/2	Moderate	0	910	0.4	7.7
H. C.	32	M	Rheumatic	1/3			1820	0.5	
M. S.	54	F	Rheumatic	1/3			1120	0.85	2.8
L. G.	35	M	Rheumatic	1/3			1300	0.3	6.8
A. B.	57	F	HCVD	1/12	Moderate	59	1680	0.8	3.5
F. H.	39	F	Rheumatic	1/3			2295	1.6	1.4
				1/2	Severe	31	1150	0.85	3.7
				3/4			1010	0.2	
				11/12		59			

CCP—Chronic constrictive pericarditis
ASHD—Arteriosclerotic heart disease
HCVD—Hypertensive cardiovascular disease
* Mercurial diuresis

given ACTH for 7 and 8 days, respectively (Fig. 5). Mercurials were administered at various intervals, and the daily urinary volumes, 17-ketosteroid, and corticoid levels determined.

Conn, Louis, and Johnston[3] on administration of ACTH to 2 normal individuals, found that a dosage of 26 mg. daily produced a two-fold increase in daily formaldehydogenic corticoid excretion and increases ranging from 15 to 80% in daily 17-ketosteroid excretion. A dosage of 50 mg. daily occasioned increases of 3 to 4 fold and 2 to 4 fold, respectively, in the daily excretion of these 2 steroids. McIntosh *et al.*[16] report results similar to Conn and coworkers on administration of 50 mg. of ACTH to a normal individual. Mason[17] obtained increases varying from 2 to 6 fold in corticoid excretion and 20 to 100% in ketosteroid excretion after giving 70 mg. of ACTH to 2 patients with rheumatoid arthritis.

F.H., on receiving a daily dose of 50 mg. of ACTH, showed an increase in ketosteroid excretion of 7 to 50%, but no increase in corticoid excretion was obtained until a mercurial diuretic was administered (Fig. 5). H.T., who had an extremely low control corticoid value, showed a definite percentage increase in the excretion of both steroids. In neither case were the absolute values per 24 hours of these steroids at all comparable to those obtained in normal individuals after ACTH administration, until mercurial diuresis occurred (Fig. 5). The circulating eosinophils fell normally in both patients 4 hours after the administration of 25 mg. of ACTH.

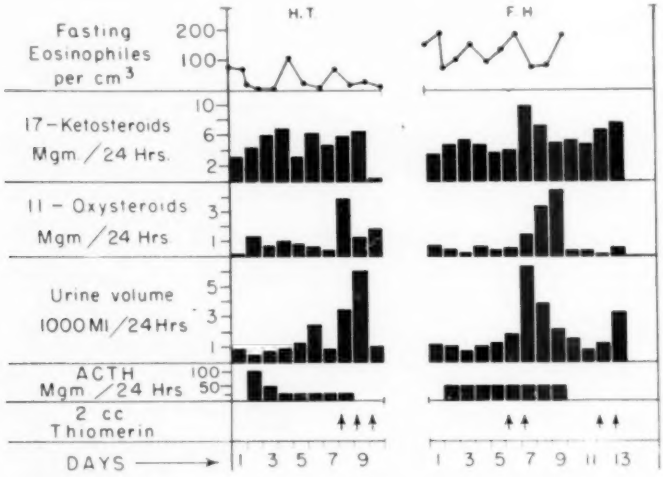


FIG. 5.—The influence of ACTH and mercurial diuretic administration on urinary 17-ketosteroid, 11-oxysteroid, and volume excretion in cardiac decompensation.

The possible influence of renal function on the level of urinary cortical hormones was investigated in 3 patients with congestive heart failure and 2 nonedematous individuals with normal cardiac function (Fig. 6). Urinary corticoids and 17-ketosteroids were determined 24 hours previous to, and 24 hours following, the intramuscular administration of a mercurial diuretic (2 cc. of thiomerin). In all patients, the

outpouring of urinary corticoids after the diuretic was marked and was, in fact, greater proportionately than the water diuresis. The nonedematous controls, however, showed relatively little change. These results are in agreement with the work of Lloyd and Lobotsky[14], who found no change in corticoid excretion with diuresis in normal individuals unless urine volumes of 5,000 to 7,000 cc. were obtained by extreme hydration, in which instances the corticoid excretion was doubled. They found, on the other hand, a corticoid increase out of proportion to the increment in urine volume during moderate diuresis in edematous cirrhotics.

In a fourth patient, 11-oxysteroid and 17-ketosteroid excretions were determined during 3 different periods in the clinical course: a) during a period of mercurial diuresis, b) 8 days after the cessation of mercurial diuresis when reaccumulation of fluid had occurred, and c) after 12 days of daily mercurial therapy when little water retention or diuresis was evident. It is apparent (Fig. 6) that the largest excretion of corticoids is coincident with maximum diuresis but is 5 times as great as other levels, whereas the urine volume is only 3 times as large.

Discussion. In this clinic, 11-oxysteroids in 25 of 31 urine samples collected from 21 normal humans without endocrine disease ranged from 0.9 to 2.0 mg./24 hours; of the 6 outside this range, 3 had values of 0.8, 2 of 2.2, and 1 of 2.4 mg./24 hours. Twenty of 23 cardiac patients (Table 1) had levels below 0.9 mg., and 17 were below 0.8 mg. Fourteen of the 15 patients who had had symptoms longer than one year showed values below 0.9 mg., and 13 were below 0.8 mg. The one value in this group that was within normal range was obtained during mercurial diuresis.

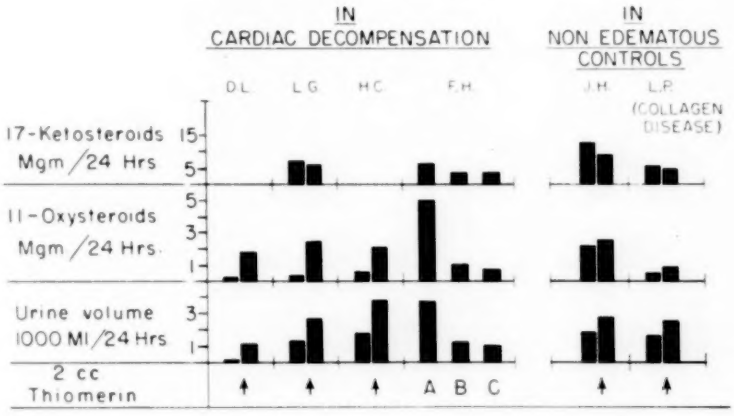


FIG. 6.—The influence of mercurial diuresis on urinary 17-ketosteroid, 11-oxysteroid and volume excretion. A, 4th day of mercurial diuresis. B, 8th day of no mercurial. C, 12th day of consecutive daily mercurial therapy.

F.H. (Table 1) exhibited a progressive decrease in 11-oxysteroid levels determined at periods of 4, 6, and 9 months after onset of her decompensation. Fig. 1, likewise, suggests that patients with symptoms of long-standing decompensation tend to have lower 11-oxysteroid excretion than those of comparatively recent onset. W.R., J.M., H.S., D.M., and M.J. exhibited mini-

mal fluid retention at the time of study but still excreted subnormal amounts of corticoids.

Normal levels of urinary 17-ketosteroids in this laboratory range from 7 to 20 mg./24 hours for males, and 5 to 15 mg./24 hours for females. Figs. 2 and 3 demonstrate the depression of 17-ketosteroid excretion found in most of these patients. Whether or not a relationship exists between the urinary levels and the duration of decompensation is not clear from these data.

The abnormally low levels of urinary hormones found in these patients may be due to decreased hormonal production from adrenal cortical insufficiency, to decreased hormonal excretion secondary to renal retention, or to a combination of both these factors. They may also result from the unlikely possibility of increased tissue utilization.

The increased effect of insulin on the blood sugars of subjects decompensated longer than 6 months, the impaired eosinophil responses to hypoglycemic stress of the majority, and the low urinary corticoid values obtained in 5 patients who had minimal fluid retention all suggest some adrenocortical hypofunction. On the other hand, the substantially increased 11-oxysteroid excretion associated with mercurial diuresis indicates corticoid retention. The small rise of urinary 11-oxysteroids after the administration of ACTH to 2 patients (Fig. 5) until diuresis had occurred is compatible with either poor adrenal response or failure of excretion of the products of adrenal stimulation. The normal eosinophil decline with ACTH does, however, indicate some cortical responsiveness. On the other hand, in case F.H., some unresponsiveness of the adrenal cortex to ACTH seems likely, since the urinary corticoid increase after ACTH and mercurial diuretic was of the same order of magnitude as that obtained by mercurial alone (Figs. 5 and 6.). The disparity between urine volumes and corticoid levels in patients H.T. and F.H. after diuresis may signify a somewhat different mechanism of excretion of corticoids from that of water. This is also suggested by the lack of good correlation between urine volumes and corticoid levels in these patients as a group; the coefficient of correlation (r) for these 2 variables was found to be +.5035, that is, the correlation was poor. A significant correlation was found to exist between urine volume and ketosteroid excretion in the male cardiacs (r= +.9246) but not in the case of the female cardiacs (r=−.3496). The small number of cases in each group may perhaps explain this discrepancy. Further investigation of corticoid excretion is now in progress.

According to Olsen and Nuetzel[19], patients with collagen, neoplastic, hepatic, and infectious diseases show insulin resistance, implying that the adrenal cortex is responding to stress with increased activity. The present studies suggest that in long-standing cardiac decompensation, the adrenal cortex is relatively refractory to stimulation and becomes progressively more so with increasing duration of the decompensation as evidenced by the increased tendency toward lowered corticoid excretion, insulin sensitivity and impaired eosinophil responses. The possibility must be considered that corticoid retention at the renal level may lead to accumulation within the organism, which in turn depresses the endogenous production of ACTH. Borstein and Trewhella[2], however, have recently reported that the reverse is true in acute decompensation. They found increased ACTH activity, assayed biologically, in the plasma of 6 acutely decompensated patients, with return to normal values following control of the decompensation. The adrenocortical in-

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sufficiency suggested by our findings in *chronic* decompensation may conceivably be on the basis of exhaustion after repeated adrenal stimulation early in the decompensation.

The changes in 17-ketosteroid excretion are even more difficult to interpret from our data. The urinary response to ACTH was below the expected, although the amounts of hormone given may have been too small, and diuresis did not consistently increase the levels of 17-ketosteroids. The reports in the literature on this subject are, likewise, contradictory. McHenry *et al.*[15] found a correlation between urinary volume and 17-ketosteroid values in normal humans. Pincus[21], on the other hand, was unable to obtain a significant increase during diuresis in one subject studied. DeKoning *et al.*[6] and Kimeldorf[12] found no correlation between daily urine volume fluctuations and 17-ketosteroid excretion in rabbits, but Danford and Danford[4], also using rabbits, were able to obtain a significant increase during diuresis.

The findings in this study suggesting adrenocortical hypofunction in chronic congestive failure may be of interest in relation to the present disagreement concerning the mechanism of salt retention in myocardial insufficiency. One group of investigators believes that the positive salt balance characteristically observed in cases of congestive failure is the result of an increased avidity of the renal tubules for salt because of hormonal stimulation. It is assumed by them that an insufficient circulation is a stressful stimulus and that the pituitary–adrenal mechanism is activated thereby. Previous reports of increased urinary corticoid excretion and of sweat secretion findings compatible with increased adrenocortical function have been used as supporting evidence.

The other school of thought, whose arguments are well summarized in a recent review by Stead[22], has claimed that the important factor in the reduced salt clearance is the marked drop in renal blood flow and glomerular filtration rate which result from the reduced output of the failing heart. An important consequence of the fall in filtration rate is a decrease in the amount of sodium chloride presented to the tubules. The latter reabsorb nearly all of the filtered salt, but the absolute amount filtered is so small that the amount reabsorbed (not the percentage) is considerably less than in the normal subject. No alteration of endocrine function would be essential in this mechanistic theory.

Our findings do not support the contention of the former group that increased adrenocortical activity is found in cardiac decompensation. On the contrary, our evidence strongly suggests decreased adrenocortical function. It is admitted that we did not study salt metabolism directly, and further, that adrenocortical hyperactivity may be present *early* in the course of the disease, but it would appear that, after congestive failure has been present for some period of time, cortical hyperactivity cannot explain the salt retention and the attendant increase in extracellular fluid volume.

Whether the progressive decline in adrenocortical function in late cases of myocardial insufficiency has any bearing on the development of mercurial resistance and on the persistence of edema in some cases, despite low sodium blood levels, cannot be determined from the data presented. If the pattern of interaction of cortical and posterior pituitary hormones postulated by Gaunt *et al.*[10] is considered in this connection, it may be that the hypoactivity of the adrenal cortex favors edema formation because of the pre-

ponderance of antidiuretic material, presumably antidiuretic hormone (ADH), as a result of the unbalanced adrenocortical–ADH relationship. It may also be that the further reduction of renal plasma flow and glomerular filtration rate beyond that incident to reduced cardiac output may be due to the glandular insufficiency. Finally, Gaunt *et al.* have suggested that cortical hormones may in some instances and under certain conditions inhibit, and in some stimulate, the reabsorption of sodium chloride, thus adding considerable complexity to any attempt at an analysis of glandular relationships in this disease. It is obvious that much further work needs to be done along these lines before clarification is possible.

Summary and Conclusions. 1. Urinary 11-oxysteroid and 17-ketosteroid excretion levels were appreciably lower than normal in the majority of 23 patients with congestive failure. The few normal levels occurred in those with decompensation of recent onset. These findings may be due to decreased hormonal excretion, decreased hormonal production, or a combination of both.

2. In edematous patients, mercurial diuresis causes an increase in excretion of 11-oxysteroids of as much as 10-fold, but in the nonedematous, only slight increases occur.

3. Eleven patients with chronic decompensation of over 6 months' duration showed increased insulin sensitivity and hypoglycemic unresponsiveness. Most of those with decompensation for 2 years or longer showed impaired eosinophil response to hypoglycemic stress.

4. After the administration of small amounts of ACTH to 2 patients in congestive failure, the expected increases in 11-oxysteroid excretion did not occur until after the administration of a mercurial diuretic, although the eosinophil responses were normal.

5. These findings suggest a retention of the formaldehydogenic corticoids at the renal level as well as the development of adrenocortical refractoriness in chronic cardiac decompensation.

6. Hormones of the adrenal cortex influence water metabolism and are necessary for efficient water excretion. It is possible that abnormalities of production and excretion in cardiac decompensation may contribute to the development and/or maintenance of cardiac edema.

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PROGRESS
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OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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ACTH AND CORTISONE IN RHINOLARYNGOLOGY

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ACTH and cortisone are drugs that intrigue all physicians, regardless of their specialized interests. Despite this, surprisingly little has thus far appeared in the medical literature with respect to the rhinolaryngologic use of these agents in the laboratory and in clinical practice. Presumably, the dearth of published communications can be explained partly by lack of availability of ample supplies of ACTH and cortisone for research purposes and as therapeutic agents.

Tissue changes in the upper respiratory tract during pituitary adrenocorticotropic hormone therapy have been studied by Bordley[1] in 47 patients with allergic diseases. Approximately 400 examinations were made on this group. Nasal polyps were removed from 5 patients for examination, while nasopharyngeal lymphoid tissue was removed from 16 patients. A total of 47 biopsies was performed at varying intervals during treatment. Routine study included palpation of cervical lymph nodes; inspection of mouth, tongue, and throat; and transillumination and roentgenoscopy of the paranasal sinuses. It was observed that during ACTH therapy the nasal mucous membranes shrink, develop a slate-pink color, and are covered with a thin layer of clear mucus. Polyps become opaque and pink and begin to shrink, disappearing completely in many instances. Such changes appear to be correlated with the initial eosinopenia developing with pituitary adrenocorticotropic hormone therapy. The nasopharyngeal lymphoid tissue becomes clearly distinct from its surrounding structures, developing an orange-pink color. Discharge around it clears up, and the crypts become more prominent. Within a few days after discontinuation of treatment, the nasal mucous membrane loses its dusky appearance, and the lymphoid tissue returns to its former state. Nasal polyps return in from 2 weeks to 2 months. Cortisone has much the same effect on the tissues of the respiratory tract as does ACTH. Nasal sprays of cortisone result in a slow but definite regression of nasal polyps.

Thorn[13] and his associates treated a patient with severe, persistent allergic rhinitis, of 2 years' duration, with ACTH, employing 10 to 12 mg. of the medicament every 6 hours for 10 days. Previously antihistaminic drugs and

hyposensitization had been but slightly effective. Improvement in nasal patency and nasal rhinorrhea was detected within 24 hours following the initial use of ACTH. Signs and symptoms of allergic rhinitis disappeared within 96 hours. Randolph and Rollins[9] observed striking amelioration of ragweed hay fever symptoms in 4 patients and complete protection for the remainder of the hay fever season in 3 of the patients after employment of ACTH. It has been noted that patients receiving ACTH and cortisone were more susceptible to the common cold while taking the hormones[7].

Samter's[11] experience with ACTH and cortisone in allergic and inflammatory disease of the upper respiratory tract is based on fairly extensive studies of patients afflicted with seasonal and perennial rhinitis, bronchial asthma, emphysema, and pulmonary fibrosis. As in rheumatoid arthritis and lupus erythematosus, ACTH and cortisone act on the shock tissue of the allergic person in an often spectacular manner: attacks of bronchial asthma subside and atopic dermatitis clears rapidly. Administration of either hormone in large dosage causes a depression of glandular function; a high blood level depresses production and release of the endogenous hormone and establishes a true hypoplasia of the glandular tissue. Hypoplasia, in turn, will result in a relative deficiency of the hormone after withdrawal of the exogenous supply and, in clinical terms, establish a recurrence of symptoms which frequently surpass the patient's pre-treatment distress. Moreover, adrenal corticosteroids inhibit physiologic response to infection. Cortisone prevents granulation, slowing the healing of wounds and endangering the normal leukocytic response. The organism consequently becomes vulnerable to infection, a fact which has caused many clinicians to administer antibiotics simultaneously with ACTH and cortisone. Samter finds the end-results of prolonged treatment with ACTH and cortisone disappointing. He believes the otolaryngologist should resist the temptation to use these hormones for any condition that responds to conservative management.

Hahn[6] and his associates studied 174 patients with acute streptococcic tonsillitis and pharyngitis to determine the effect of cortisone on the disease and on the subsequent incidence of rheumatic fever. The patients were divided into treated and control groups. Two treatment schedules were employed. Seventeen patients received a total of 500 mg. of cortisone intramuscularly in 50-mg. doses, while 70 patients were given a total of 600 mg. in 100-mg. doses. Patients in the control group received injections of 0.85% sodium chloride. With the exception of codeine, which was prescribed for the relief of severe headache, no antipyretics or other medicaments were given. Patients were examined daily through the sixth day of illness by one member of the staff who had no knowledge of the type of treatment administered. Cortisone therapy had no effect on symptoms or physical signs of this infection. Patients who received cortisone had fever for a longer period than the control patients. Suppurative complications developed in 1 of the treated patients and in 3 of the control subjects. Rheumatic fever was diagnosed in 2 treated patients and in 5 control subjects. The increase in the antistreptolysin titer was somewhat less in the serums of the treated group than in the control patients 1 week after the onset of infection, but at 2, 3 and 4 weeks the formation of antibody was slightly greater in treated than in control patients.

In general, patients suffering from hemolytic streptococcic infections of the respiratory tract frequently develop a variety of disorders as a complication of their illness. Skin manifestations, polyarthritis, involvement of the heart and its structures, persistent fever, general toxicity, and nephritis may develop in from 3 to 30 days after the respiratory infection begins. In approximately 20% of such respiratory tract illnesses, a disorder supervenes which cannot be explained on the basis of increased reaction of the primary inflammatory site or as a result of invasion of remote tissues by the hemolytic streptococcus. These complicating nonsuppurative sequelae of hemolytic streptococcus disease have been referred to as the poststreptococcic state. It has been suggested that the poststreptococcic state occurs not as the result of the primary etiologic agent per se, but rather as a more complex mechanism by which the patient's tissues have been sensitized to some fraction or product of the hemolytic streptococcus, probably as a result of previous exposure to the organism.

Doerner[4] and his associates present a case demonstrating the classical features of the poststreptococcic state and emphasize the efficacy of cortisone in the treatment of this condition. The case reported describes the development in a young white woman of a typical hemolytic streptococcus infection of the throat. Despite early and adequate antibiotic therapy, she continued to manifest prolonged unremitting fever. Subsequent complications included a scarlatiniform rash, transient arthritis of the knee and ankle, a mitral systolic murmur, a transient pericardial rub, left lower lobe pneumonia and pleural effusion, anemia, leukocytosis with pronounced neutrophilia, progressive generalized toxicity, and extreme debility. As the patient failed to respond satisfactorily to specific antibiotics, salicylates, and general supportive measures, cortisone was administered. This was immediately followed by the rapid disappearance of all of the features of the poststreptococcic state.

An attempt was made by Freeman[5] to evaluate the action of cortisone on laryngeal edema secondary to a course of protracted fractional irradiation for carcinoma of the larynx. A striking response resulted, inasmuch as within 11 hours the edema diminished noticeably and within 4 days the edema was considered minimal. No antibiotic or chemotherapeutic agents had been given. A second patient with laryngeal edema of similar pathogenesis was treated in like fashion, with equally impressive results. Cortisone was also administered to 4 patients with subglottic edema. In 2 patients, indirect laryngoscopy was performed without difficulty. The subglottic edema diminished markedly in both patients within 12 to 24 hours. Although laryngoscopic examination was not attempted in the remaining 2 patients, clinical improvement was detected within 12 hours. All 4 patients received antibiotics and steam inhalations prior to and during administration of cortisone. A patient with supraglottic edema secondary to a foreign body was also given cortisone, and within 12 hours inspection of the larynx revealed pronounced diminution of the edema. Prior to cortisone medication, antibiotics had been administered for a period of 36 hours, without noticeable response. All of the patients were hospitalized because of the threat of impending asphyxia. In all patients but one, cortisone was given orally in full dosage. Toxic effects due to fluid retention were observed in 1 patient following prolonged administration of

cortisone. This was satisfactorily controlled by administration of diuretics.

Nebulized cortisone was employed by Reeder and Mackey[10] in treating a 60-year-old male with type VII pneumoccic pneumonia. A total of 25 mg. of cortisone was diluted with 4 cc. of isotonic sodium chloride solution, and 1 cc. of the mixture was given as an aerosol every half hour for 33 hours. This was followed by the administration of aureomycin for a period of 9 days. Rapid subjective improvement and a drop in temperature resulted from the administration of cortisone. The pulmonary disease process was apparently unaffected. Although the reaction of the host to the disease was favorably influenced, the bacterial agent was not influenced. Inhalation of cortisone appeared to be as effective as parenteral administration. Inhalation of cortisone in the dilution employed does not appear irritating to trachea or bronchi.

Observations on the effect of ACTH and cortisone on bronchial asthma and hay fever indicate their usefulness in these disease entities. According to Segal and Herschfus[12], the goal of all therapy in the patient with serious bronchial asthma is the production of a prolonged remission. ACTH apparently offers a way to cause a remission more consistently than many other therapeutic regimens. However, improvement with ACTH may frequently be maintained but for a short period; prolonged administration is not feasible; there is some evidence that in relapse the symptoms of some types of hypersensitivity may recur with greater severity than before; and repeated stimulation of the hypothalamus–pituitary–adrenal axis may not be desirable. To what extent undesirable physiologic and toxic effects following in the wake of ACTH and cortisone therapy will limit their usefulness in the management of the more chronic allergic disorders remains to be revealed.

In their study, Segal and Herschfus administered 27 courses of ACTH therapy to 20 patients with severe chronic bronchial asthma over a period of 8 months. There were 14 females and 6 males, all seriously ill with a wide variety of associated and related defects, including hay fever, nasal polyps, sinusitis, severe bronchitis, emphysema, hypertension, cerebral arteriosclerosis, and diabetes mellitus. The immediate therapeutic effect in the 27 patients was summarized as follows: failure, 2; fair, 4; good, 3; and excellent, 18. The continued therapeutic effect was as follows: failure, 3; fair, 8; good, 10; and excellent, 6. The period of remission generally was short. Repeated intensive courses of therapy were frequently required and appeared more effective than attempts at maintenance therapy. Failure to respond to the same degree was sometimes noted at the conclusion of the second course of therapy. It is believed repeat courses of therapy should not be employed too freely, inasmuch as the nature of the repeated remission and the effects of repeated hormonal overstimulation may prove hazardous.

The effect of cortisone on 3 patients afflicted with hay fever and seasonal asthma due to ragweed pollen has been described by Carryer[3] and his associates. The patients received 100 mg. of cortisone or 100 mg. of cholesterol crystals (as a control) daily for 4 weeks. Results were considered beneficial, each patient experiencing prompt relief. Symptoms of bronchial asthma were relieved more rapidly than those of hay fever. Only mild, transitory symptoms persisted after 3 days of treatment with cortisone. However, symptoms recurred shortly after cessation of medication. Randolph and Rol-

lins[9] treated 5 patients afflicted with bronchial asthma with cortisone. In 4 patients they made comparative studies of ACTH and cortisone, finding the latter partially effective in relieving the symptoms of intractable asthma, but in the dosage employed, less effective than ACTH. Both cortisone and ACTH caused hematologic changes. One patient obtained no relief with cortisone at first but responded satisfactorily when Vitamin C was administered intravenously. Segal and his associates, however, were unable to potentiate or prolong the effects of ACTH with intravenous cevitamic acid. Randolph and Rollins observed striking amelioration of ragweed hay fever symptoms in 4 patients and complete protection for the remainder of the season in 3 of the patients following the use of ACTH.

ACTH and cortisone are not substitutes for allergic management, either in adults or children. These drugs do not constitute the first line of therapeutic approach in the treatment of an allergic patient. In an acute allergic emergency (immediate serum reaction, anaphylactic shock, or acute asthma) the hormones do not work rapidly enough to save the patient's life. ACTH and cortisone are useful measures in special allergic situations, but they should not be employed as a short cut to a careful diagnosis and more rational therapy[8]. Burrage[2] cautions that despite the dramatic temporary cessation of symptoms observed with ACTH in allergic diseases, one should not hastily conclude that the problem of allergy is about to be solved.

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DERMATOLOGY AND SYPHILOLOGY

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THE L.E. CELL AND PHENOMENON IN LUPUS ERYTHEMATOSUS

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IN spite of much conjecture[30] and observation the basic nature of lupus erythematosus, especially the acute disseminated (systemic[1,14c]) type, remains an enigma[22,24,28,33]. Therefore, any fundamental discovery which promises to aid in the definition of even one phase of this disease concept is eagerly received. The latest of these is the L.E. cell and phenomenon. Sulzberger and Baer[31] have actually declared that "the demonstration of the L.E. cell and the further studies concerning this cell, its causes and the mechanisms of its formation, as carried out by Hargraves and by Haserick and his co-workers, constitute one of the most brilliant accomplishments of dermatology". With this we heartily agree although, in all fairness, the credit goes not only to dermatologists, but to internists and hematologists as well.

Although the L.E. cell has been known for only about 3 years, the intense interest in the phenomena of its production is so great that a brief statement of the present status of our knowledge is in order. Previous summaries have been made by Hamburger[11], by Touraine[34], by Barnes and his colleagues[3a], by Vilanova and De Dalento[36], by Berman and his colleagues[4], and by Haserick[4c]. Because of the newness of the observations, insufficient time has elapsed to allow a really critical appraisal of the significance of the L.E. cell and phenomenon. Although it would appear generally permissible to consider this cell and phenomenon as valuable in the diagnosis of systemic lupus erythematosus, the material will be presented in a more or less chronological order (cf. Arnold[1b])*.

Discovery of the L.E. Cell. In January, 1948, Hargraves, Richmond, and Morton[13] presented their experience over 2 years (since 1946) with 2 bone marrow elements: the "tart" cell and

* A new phenomenon which may or may not be dependent on the same factor as the L. E. cell and phenomenon has been reported by Schleicher[27]. This is the erythrocyte aggregation factor in the plasma and serum of patients with acute lupus erythematosus.

the "L.E." cell, which they believed had never been described in the literature. Although they did not know the significance of their observations, they felt impelled to describe the involved cells.

"The first cell we have called a 'tart' cell in our laboratory. We have used the term for such a long period that it seems a fitting name to apply to it. This cell, we have found, can occur in practically all bone marrows; however, it is usually present in increased numbers in bone marrow preparations from patients suffering from a serious illness such as lymphoblastoma, pulmonary infection or metastatic carcinoma or in cases in which the diagnosis is obscure. This cell usually is a histiocyte or a 'monocytoid reticulo-endothelial' cell that contains a second, characteristic nucleus usually placed in the Hof of the primary nucleus. This second nucleus nearly always stains reddish purple with Wright's stain in contrast to the dark purple nucleus of the histiocyte. This secondary nucleus shows a sharp nuclear membrane and the chromatin is definitely visible in a thick structural arrangement with relatively sharp differentiation between the chromatin and the parachromatin. Occasionally a cell is seen in which there are 2 such secondary nuclei, so that practically the entire cytoplasm is occupied by nuclear bodies. Except for this secondary nucleus the cell seems not to differ in appearance from the other histiocytes observed in bone marrow preparations. One can see this same phenomenon occurring in a mature neutrophilic polymorphonuclear leukocyte and less commonly in an eosinophil.

"We have the impression that this is probably an abortive nucleus resulting from a previous incomplete mitotic division of the cell. In numerous instances we have seen this secondary nucleus partially outside of the cell and it is impossible to say whether it is being extruded from the cell or is in the process of being taken into the cell. The fact that we have seen this secondary nucleus in the eosinophils would argue against the latter assumption. The distinguishing feature of this cell, which must be emphasized here, is that the secondary nucleus has retained a definite chromatin structure. Once this cell has been observed it will be found, as stated previously, in small numbers in many bone marrows.

"The second cell which we wish to present has been called an 'L.E.' cell in our laboratory because of its frequent appearance in the bone marrow in cases of acute disseminated lupus erythematosus. This cell undoubtedly represents a process which is going on in such bone marrows and is the end result of one of two things: either phagocytosis of free nuclear material with a resulting round vacuole containing this partially digested and lysed nuclear material or, second, an actual autolysis of one or more lobes of the nucleus of the involved cell so that it presents essentially the same appearance as the one which has phagocytized nuclear material. The 'L.E.' cell is practically always a mature neutrophilic polymorphonuclear leukocyte in contradistinction to the 'tart' cell, which is most often a histiocyte. It seems obvious that the chromatin material is within a large phagocytic vacuole and all gradations of digestion of this material have been observed. While most of these cells characteristically show a homogeneous, purple-staining mass in the vacuole, there are instances in which the chromatin pattern is still visible. For this reason it is essential that this cell be differentiated from the 'tart' cell described in an earlier paragraph. Ordinarily this can be accomplished by finding numerous 'L.E.' cells in which the process of digestion has altered the appearance of this chromatin material, ranging from small smoky remnants of 'digested' material to relatively intact nuclei indistinguishable from the secondary nucleus of the 'tart' cell."

They surmised that these cells were only the result of a lytic–phagocytic phenomenon. They did not find either of the cells in the peripheral blood. To the date of publication they found this phenomenon only in the bone marrow in certain cases of acute disseminated lupus erythematosus.

Development of Techniques for Discovery or Inducing of L.E. Cells. In September, 1948, Haserick and Sundberg[18] reported the first of a number of studies emanating from the Cleveland Clinic. These and a number from other quarters have done much to elucidate the significance, mode of production, and other aspects of the L.E. phenomenon. Thus the phenomenon not only appears in bone marrow but in the circulating blood, clotted blood, and blister fluid.

In their first study, Haserick and Sundberg[18] found the L.E. cell present in 4 out of 5 cases of acute lupus erythematosus but not present in 2 cases of subacute and 3 of chronic discoid lupus erythematosus, or in 3 cases of dermatomyositis and numerous cases in which leukopenia was a prominent feature. From these observations Haserick and Sundberg concluded that the L.E. cell was a valuable diagnostic aid in acute disseminated lupus erythematosus, that these cells are found in largest numbers during the severe stages of the disease, and with difficulty during remissions, and that the greatest value of the L.E. cell was its possible presence in suspected cases of acute disseminated lupus erythematosus in which the usual cutaneous manifestations are absent.

Sundberg and Lick[32] early in 1949 reported for the first time the presence of "L.E." cells in smears of the concentrated leukocytic layer of venous blood in 3 cases of acute disseminated lupus erythematosus. These investigators emphasized that "L.E." cells are not found with sufficient ease in the circulating blood to make this method of confirming or establishing the diagnosis of acute disseminated lupus erythematosus as practical as that of examining smears of bone marrow. They felt it worth while, however, to examine the blood for the purpose of confirming the diagnosis of acute lupus erythematosus in a patient who is extremely ill, so as to make this the method of choice from the standpoint of the hematologist and the patient.

In April, 1949, Hargraves[12] reported the production *in vitro* of the L.E. cell phenomenon. He employed normal bone marrow elements and blood plasma from patients with acute disseminated lupus erythematosus. He stated that further observations, according to Hargraves, lend weight to the hypothesis that Libman-Sacks disease, or acute lupus erythematosus, is a result of hypersensitivity. The L.E. phenomenon is evidently immunologic in nature. He predicted that a positive finding in examination of smears of peripheral blood would have a significance comparable to that of a similar finding in examination of bone marrow. Klemperer, Gueft, and Lee[19] in 1949 observed hematoxylin-staining bodies in the heart, lymph nodes, kidney, and other sites (mesenchymal tissues) of 3 cases of acute lupus erythematosus. These were similar to those found in various manifestations of lupus erythematosus previously by Gross[10] in 1932, Ginzler and Fox[8] in 1940, and by Klemperer, Pollack, and Baehr[20] in 1941. Re-examination of the material of 34 cases of lupus erythematosus yielded the hematoxylin-stained bodies in one or more sites in 31 cases. Studies made by Klemperer's group indicated identity in the nature of the phagocyted material of "L.E." cells with the small hematoxylin-stained bodies. Histochemical studies identified these bodies as nucleic acid. This group of investigators believes that one of the factors in acute lupus erythematosus is a disturbance of nucleic acid metabolism of the cells of the mesenchyme manifesting itself in depolymerization of the desoxyribose nucleic acid.

In August of 1949 Haserick and Bortz[15b] tried to answer the question of whether the L.E. cell was a primary cytologic alteration or was secondary to some change in the blood. They devised a method by means of which it is possible to induce chemotaxis of polymorphonuclear leukocytes and the L.E. cell in bone marrow preparations with plasma or serum of patients acutely ill with disseminated lupus erythematosus. Normal plasma, hyperglobulinemic plasma from a patient with cirrhosis, and plasma from patients

with chronic discoid lupus erythematosus failed to produce the phenomenon. Haserick and Bortz[15a], using plasma from 14 patients with acute lupus erythematosus, confirmed this experience by inducing the L.E. cell and clumping of polymorphonuclear leukocytes in the bone marrow of 48 normal patients. They also failed to induce this phenomenon utilizing plasma from patients with chronic discoid lupus erythematosus, cirrhosis, scleroderma, or rheumatoid arthritis. They felt their data permitted the conclusion that:

1. Plasma from patients with acute disseminated lupus erythematosus contains a substance which regularly induces the L.E. cell and clumping of leukocytes in normal marrows.

2. The L.E. cell observed in the bone marrow of patients with lupus erythematosus is therefore a secondary rather than a primary phenomenon.

3. The L.E. plasma–normal bone marrow preparation is a valuable diagnostic test in acute disseminated lupus erythematosus.

4. The plasma–marrow test is an indicator of severe systemic involvement in lupus erythematosus.

5. The L.E. plasma–normal bone marrow mixture merits consideration as a useful investigative tool.

The St. Louis group (Barnes, Moffatt, and Weiss) have made important contributions to the developing knowledge of the L.E. phenomenon. In March, 1950[23], they described a method of producing L.E. cells by using the plasma of acute lupus erythematosus patients mixed with the white cells obtained by centrifugation of blood from normal persons. In a later study these workers[3a] simplified their method so that an anticoagulant was not needed. In an addendum to this article the authors report certain unpublished work of Harry Agress dealing with the production of the L.E. phenomenon in the absence of anticoagulants. He has demonstrated L.E. cells and rosettes in abundance in fixed stained sections consisting of clotted sternal marrow elements untouched by anticoagulants and obtained from a patient in a moribund state with acute disseminated lupus erythematosus. He also demonstrated what are thought to be extracellular L.E. bodies in the same preparations. These bodies are reported to be identical morphologically and to date have shown the same staining properties as those bodies found lying in L.E. cells and the rosettes.

Madden[21] in his comparison of muscle biopsies and bone marrow examinations in dermatomyositis and lupus erythematosus made the pertinent observation in agreement with all observers that the L.E. cells were found only in patients with acute disseminated lupus erythematosus and that the number of these cells decreased as the systemic symptoms subsided. This observation was based on a study of the literature and of 16 patients with lupus erythematosus (8 with the acute and 8 with the chronic form). He also observed that L.E. cells are not always present in acute disseminated lupus erythematosus. (They were present in 7 of 11 of Morton's patients; 4 of 5 of Haserick and Sundberg's patients; 5 of 7 of Montgomery and McCreight's patients, and 4 of 8 of his own patients. Suksta and Conley[33a] found L. E. cells in 14 of 21 cases of disseminated lupus erythematosus but these cells were not observed in any other condition. In patients treated with ACTH or cortisone the L. E. cells and rosettes decreased in number but did not disappear.) Furthermore, Madden correlated the finding of L.E. cells with the prognosis. The 4 patients who showed L.E. cells

in the bone marrow were alive at the time his report was written, while the four whose bone marrow did not show L.E. cells were dead. Madden points out that this observation is at variance with the findings of Montgomery, of Brunsting and others of the Mayo Clinic Group, who indicated that the presence of L.E. cells was a poor prognostic sign. Since lupus erythematosus is usually fatal, the value of the L.E. cell in prognosis is difficult to assess. The presence of the cell in a fair number of patients with acute lupus erythematosus makes the cell of certain diagnostic value. It is especially valuable when present in differential diagnosis between dermatomyositis and lupus erythematosus, particularly in those unusual instances of visceral lupus erythematosus without cutaneous lesions.

Fisher and Moyer[6] reported a series of experiments in which various combinations of normal oxalated blood and L.E. plasma were mixed. According to Berman *et al.*[4], Fisher and Moyer did did not report observations on control material consisting of mixtures of normal plasma, normal blood leukocytes, and blood-bank autolysates. These were carried out by Berman's group. When normal plasma was used in place of L.E. plasma, typical L.E. cells were not found. The experiments suggest the activity of a factor in L.E. plasma which promotes or enhances phagocytosis of nuclear debris by leukocytes from normal blood.

In May, 1950, 2 studies of the L.E. cell appeared: the one by Berman and his co-workers[4] on the so-called "lupus erythematosus inclusion phenomenon" of bone marrow and blood, and the other by Hamburger[11] on induction of the lupus erythematosus cell *in vitro* in peripheral blood. Hamburger attempted to produce the L.E. cell in the peripheral blood by incubating the cellular elements of normal white blood with plasma from patients with acute disseminated lupus erythematosus. He was successful in finding the L.E. cell in the peripheral blood of patients with acute disseminated lupus erythematosus and he could induce the L.E. cell by cross incubation of cellular elements from normal peripheral blood with the plasma of a patient with lupus erythematosus, thus simplifying the test for acute disseminated lupus erythematosus. This method is similar to that described by Moffatt, Barnes, and Weiss who also, as previously reported, had produced L.E. cells by mixing the plasma of a patient with acute lupus erythematosus and the white cells of the blood of normal persons.

Berman and his colleagues have reviewed the status of the L.E. cell to the time of writing and have added considerable original information, especially of a technical nature and of the diagnostic value of the L.E. cell. For details this paper should be consulted. Berman and his group summarize their original observations as follows:

"1. Splenectomy had no effect on the occurrence of the L.E. phenomena in marrow smears from a patient with acute lupus erythematosus, nor was there any change in the activity of the L.E. factor, as observed in the *in vitro* reaction.

"2. The post-mortem serum in acute lupus erythematosus gave positive results in the *in vitro* test.

"3. In some instances there is apparent augmentation of the L.E. plasma activity after its use in the *in vitro* test.

"4. The *in vitro* reaction obtained with the use of L.E. plasma can be observed when the test cells are of animal origin.

"5. The activity of the L.E. plasma resides in the gamma globulin fraction."

The techniques of the various procedures worked out by Berman's colleagues are quoted as follows:

TECHNIQUE FOR THE IN VITRO TEST FOR THE L.E. FACTOR. The materials required are citrated, oxalated, or heparinized specimens of the plasma to be tested (usually 0.5 cc. for each test), specimens of fresh heparinized aspirated bone marrow (human or animal). The plasma may be stored in sterile containers in the freezing compartment of an ordinary refrigerator and brought to room temperature before being tested. Equal portions of the aspirated marrow and the plasma to be tested are mixed by gentle shaking for 1 minute in a serologic test tube. The mixture is then transferred to Wintrobe hematocrit tubes, and centrifuged at 2000 rpm (standard head, radius 5¼ inches) for 5 minutes. The buffy layer is removed, together with an equal volume of supernatant plasma, and this material is stirred on a paraffin-lined watch glass. Smears are made from this mixture. They are immediately air-dried, then stained with Wright's stain. Control specimens can be prepared by substitution of the plasma being tested by (1) normal plasma, and (2) a known active L.E. plasma. The time consumed in preparation of the specimens affects the incidence of the L.E. phenomena, there being a tendency for an increase as more time elapses. In our hands the entire procedure is completed within 15 to 20 minutes. For comparative quantitative studies, the factor of time can be eliminated from consideration by adopting constant waiting periods between successive steps of the procedure or, as is the custom in this laboratory, the test materials and control materials are processed simultaneously.

TECHNIQUE FOR STUDYING "AUGMENTATION EFFECT." The procedure is identical with that outlined above, with the exception that after the specimens are centrifuged in the Wintrobe tubes, the supernatant plasma is removed and re-centrifuged at 4000 rpm. for 30 minutes. The supernatant clear plasma is stored for future use as once-used plasma. Control studies are carried out with samples of the original previously unused plasma.

USE OF ANIMAL MARROW AS THE SOURCE OF TEST CELLS. Our material is obtained from normal laboratory animals sacrificed by asphyxiation or air embolism. A long tubular bone is cracked open, the marrow is removed and immediately mixed with an approximately equal volume of the plasma being tested. Further processing is carried out as outlined above.

Stitch[29] found L.E. cells in the bone marrow of a single case of lupus erythematosus. Van Doormaal and Schreuder[35] found the L.E. cell in pleural effusion. Rebuck and Berman[26] produced the L.E. phenomenon in human skin by injecting the plasma of a patient with acute lupus erythematosus.

Gonyea, Kallsen, and Marlow[9] found L.E. cells in a clotted blood specimen after the cells had disappeared from the oxalated blood specimen, thus eliminating the possibility that this phenomenon is dependent on the use of anticoagulant.

Moyer and Fisher[25] produced L.E. cells experimentally by incubation of a mixture of living neutrophils, altered lymphocytic nuclei, and the L.E. plasma factor. The results observed under these conditions suggest that the L.E. inclusions originate from lymphocytic nuclei, whereas polymorphonuclear leukocytes did not provide similar inclusions.

Barnes, Moffatt, and Weiss[3b] reported an inclusion body that appeared in the course of their studies on the induction of the L.E. phenomenon in normal leukocytes. They felt that these objects could be stages in the evolution of the L.E. body, and further studies seem to have substantiated this idea. In a summary study, Barnes, Moffatt, Lane, and Weiss[2] have repeated and confirmed the work of previous investigators with regard to the L.E. phenomenon. They feel this phenomenon is specific and outline a staining method they have found of use in demonstrating the L.E. phenomenon and oval bodies. We quote an abbreviated technique, used by Weiss and separately distributed by the Dermatological Departments of the Barnard Free Skin and Cancer Hospital and the School of Medicine, Washington University, St. Louis, Missouri.

TECHNIQUE OF THE IN VITRO TEST FOR THE L.E. PHENOMENON (BARNES-MOFFATT TEST). The Barnes-Moffatt test is a simplified means of demonstrating the L.E. Phenomenon and, in our hands, has been proved to be 100% accurate in the diagnosis of the acute form of disseminated lupus erythematosus; in about 30% of the cases of the subacute form of the disease the test is also positive. It is negative in all cases of discoid lupus erythematosus.

Method. Draw 20 cc. normal venous blood from a volunteer and immediately defibrinate by stirring with sterile applicators in a wide, sterile test tube for about 10 minutes.

Pour off into a centrifuge tube, centrifuge for 8 minutes at 2000 RPM.

Remove buffy coat with a capillary pipette

In a Kahn dilution tube place 12 drops of the buffy coat and 12 drops of the patient's serum. With occasional gentle agitation allow to stand in the tube at room temperature for 20 minutes. Withdraw the mixture from the tube with a capillary pipette and place in a Wintrobe (hematocrit) tube. Centrifuge the mixture for 5 minutes at 2000 RPM in a Wintrobe tube.

Remove buffy coat with a capillary pipette.

Place a drop of the buffy coat on each of 3 clean glass slides, smear in the usual manner, and dry in the air.

Staining. Flood slides with Wright's stain for 2 minutes.

Add Wright's phosphate buffer solution to each slide for an additional 2 minutes.

Pour off Wright's stain and flood slides with Giemsa stain for 6 to 7 minutes.

(A supply of fresh Giemsa stain is prepared in a small glass beaker. This diluted Giemsa stain is made by using 9 drops of stock Giemsa stain and 3 cc. of Wright's phosphate buffer for each slide to be stained.)

Wash slides with distilled water, air dry and examine. In examining under the microscope if only a few L.E. cells are present they are most likely to be located on the fringes of the smears near the tails. Look for clumping, rosettes and L.E. cells.

Recently Watson, O'Leary and Hargraves[37] of the Mayo Clinic have made further observations which may further simplify the diagnosis of acute disseminated lupus erythematosus. These investigators made a differential smear of cantharides blister fluid in 5 cases of acute disseminated lupus erythematosus containing a peculiar neutrophilic leukocyte. This cell contains one or several bluish bodies and resembles an L.E. cell such as that found in material obtained on sternal aspiration from patients with acute disseminated lupus erythematosus. This peculiar neutrophilic leukocyte was not seen in smears of cantharides blister fluid from normal persons or in the blister fluid from patients with other disease. The authors had further experience with 12 additional patients with acute and subacute lupus erythematosus on whom cantharides blisters were produced and aspiration of sternal marrow was done. This peculiar neutrophilic leukocyte was found in direct smears of fluid from cantharides blisters in each case. However, they found L.E. cells in special preparations of sternal marrow in only 9 cases. Thus, in 3 cases the artificial blister fluid test seemed to be a more sensitive indicator of subacute disseminated lupus erythematosus than was examination of the sternal marrow.

The following summarizes in outline form the occurrence or production of L.E. cells as detailed above:

Mechanism of L.E. Cell Formation. The nature of the mechanism underlying the production of L.E. cells or the L.E. phenomenon is practically unknown. Fisher and Moyer[6] have suggested that 3 elements are necessary for the formation of L.E. cells: 1) active neutrophils, 2) nucleoprotein, and 3) the L.E. plasma factor. Active neutrophils apparently ingest nucleoprotein in the presence of the L.E. plasma factor. The L.E. plasma factor appears to be present in the gamma globulin fraction (Berman *et al.*[4], Haserick and Lewis[16], Haserick, Lewis and Bortz[17], Haserick[14a]). Haserick, Lewis and Bortz[17] showed that the L.E. factor disappears from the blood during intermissions and reappears during relapse in patients with acute disseminated lupus erythematosus. Haserick[14] has

SUMMARY OF OCCURRENCE OR PRODUCTION OF L.E. CELLS

L.E. Cells found in heparinized bone marrow of lupus erythematosus patient			Hargraves *et al.*, 1948[13]. Haserick and Sundberg, 1948[18].
Lupus erythematosus peripheral blood (venous)	(heparinized blood) (oxalated blood) (centrifuged)	concentrated leukocytic layer	Sundberg and Lick, 1949[31]. Hargraves *et al.*, 1949[12].
	in clotted blood of patients with L.E.		Gonyea *et al.*, 1950[9].
Produced *in vitro*	normal bone marrow (human) and L.E. plasma		Hargraves, Apr. 27, 1949[12]. Haserick and Bortz, Mar. 25, 1949[15].
	normal bone marrow (animals) L.E. plasma		Berman *et al.*, 1950[4] (dog) Sundberg[31].
	cellular elements of normal white blood plus L.E. plasma)		Hamburger, 1950[11]. Fisher and Moyer, 1950[6]. Moffatt, Barnes, Weiss, 1950[23]
In Skin	Cellular elements of normal white blood plus L. E. plasma) (no anticoagulant)		Barnes, Moffatt and Weiss, 1950[3].
	Inoculation of normal skin by L.E. plasma		Rebuck and Berman, 1950[26].
	Cantharides blister in patients with acute lupus erythematosus)		Watson *et al.*, 1951[37].

also seen a patient with acute lupus erythematosus with negative L.E. test which turned positive after treatment with cortisone. Haserick and Sundberg[18] believed that the inclusion of the L.E. cell is protein in nature and of lymphocytic origin (Moyer and Fisher[25]). Damashek and Bloom[5] have made histochemical studies to support this idea. The inclusion bodies are Feulgen-positive, indicating a possible nuclear origin. In their study, Berman and his associates noted the existence of free cloudy masses, identical with those seen within L.E. cells. They believed that, in addition to nuclei of lymphocytes, these may be derived from nuclei of other cells, including neutrophils. Moyer and Fisher's[25] investigations support the impression that the L.E. cell may be the result of phagocytosis of an altered lymphocytic nucleus, usually by a neutrophil. Gausewitz, Jones, and Worley[7] recently reported a case of moniliasis with L.E. cells. This raises the question whether these were really L.E. cells or were a simulation of the lupus erythematosus phenomenon by materials of fungal origin, such as were reported by Haserick[14d]. This latter author found that fungi, particularly of the *Aspergillus* group, induce an alteration closely resembling the lupus erythematosus phenomenon when added to heparinized bone marrow preparation. He observed rosettes of clumped leukocytes and phagocytic cells of the L.E. cell type.

Lee and his co-workers[20 a, b] have devised a method for demonstrating the presence of L. E. cells. It is simpler to perform and more sensitive than other methods. It permits clearcut distinction between bloods which show the L. E. phenomenon and those which do not produce L. E. cells.

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BOOK REVIEWS AND NOTICES

THE KIDNEY: MEDICAL AND SURGICAL DISEASES. By ARTHUR C. ALLEN, M.D., Pathologist, James Ewing Hosp., New York City. Pp. 583: 1115 ills. New York: Grune & Stratton, 1951. Price, $15.00.

THIS volume is an encyclopedia of kidney pathology, with a tremendous accumulation of illustrations (1115) of every type of medical and surgical renal disease. Written primarily from a pathologist's standpoint, the author has achieved his goal of presenting a dynamic rather than a static descriptive treatment of this subject, and of avoiding the pitfall of oversimplification in his interpretation of renal pathology.

This book will be of greatest value to the renal physiologist and pathologist and to the research worker in these fields. However, the well integrated method of presentation of clinical, physiological, and pathological relationships recommend it to the special attention of the urologist, internist, and pediatrician.

It will be some time before a more competent or complete work in this field is written. K. C.

SPATIAL VECTOR ELECTROCARDIOGRAPHY. Clinical Electrocardiographic Interpretation. By ROBERT P. GRANT, M.D., National Heart Institute, Bethesda, Md., and E. HARVEY ESTES, M.D., U.S. Naval Hosp., Bethesda, Md. Pp. 149; with 41 ills. Phila. and New York: Blakiston Co., 1951. Price, $4.50.

EVERYONE interested in recent electrocardiographic developments should be familiar with this book, the first in English, on spatial vector electrocardiography. It is based upon the concept, long championed and developed by Duchosal and Sulzer, that for clinical purposes, the electrical forces of the heart may be regarded as an equivalent dipole for all electrocardiographic leads. Grant's contribution consists in demonstrating how the mean spatial vectors and loops can be derived from the conventional electrocardiographic leads. The book is a simplified presentation of the subject and the authors admit that there may be "inaccuracies, generalizations and dogmatisms". The book is divided into Part I, The Spatial Vector Method of Interpretation, and Part II, Clinical Applications of the Spatial Vector Method.

It should be obvious to the reader, although it is apparently ignored by Grant, that since the vector loops are translations of the electrocardiographic leads, there must be at least as many patterns of loops as there are sets of leads. Actually there are infinitely more because each loop is capable of forming an infinite number of leads so that the omission of leads produces a derived loop that is artificially smooth. Although occasional statements are made concerning the characteristics of loops, Grant, in the main, avoids this issue by assuming that the angles formed by the vectors of QRS, ST, T and by the 0.04 seconds vector to that of QRS are the clinically significant determinations. He regards the fact that the electrocardiographic leads are not on the same plane and that they are not taken simultaneously as clinically insignificant.

He believes that his method is capable of determining the spatial angle within 5° but nowhere gives an example of the determination of a specific spatial angle. He assumes an error of less than 5° is clinically insignificant. Unfortunately, only obvious electrocardiographic abnormalities are illustrated so that nowhere does he prove his statement that his method is diagnostically superior to that of conventional electrocardiography. He apparently assumes that in disease there cannot be a proportionate change in the same direction of the QRS and T vectors. The explanations for the abnormal angles are in general derived from those given for homologously abnormal conventional electrocardiographs. For instance, the abnormal 0.04 second vector is obviously a translation of the conventionally accepted duration of a significantly abnormal Q wave.

This book is recommended for the excellent insight it gives into the gross nature of the spatial vector electrocardiogram without the aid of special apparatus. The reviewer believes, however, that undue emphasis has been placed upon the correlation of the mean vectors with the anatomic location of their sources, particularly in the abnormal. The reviewer also believes, contrary to Grant's opinion, that a more accurate method of reproducing the spatial vector electrocardiogram is needed to separate on empirical grounds, just as electrocardiographic patterns were, the normal from the abnormal. Once this has been done, it is hoped that the interpretation of the loops will be simpler and more definite than the interpretation of present day electrocardiograms. L. S.

CLINICAL UNIPOLAR ELECTROCARDIOGRAPHY. By BERNARD S. LIPMAN, M.D., Asst. in Med., Emory Univ. Sch. of Med., Atlanta, Ga., and EDWARD MASSIE, M.D., Asst. Prof. of Clin. Med., Washington Univ. Sch. of Med.; Director, Heart Station, Barnes Hosp., St. Louis; Director, Cardiovas. Clinic, Washington Univ. Clinics. Pp. 230; 191 ills. Chicago: Year Book, Inc. Price, $5.00.

THIS manual is an outgrowth of a booklet prepared for the students of Washington University School of Medicine. The authors succeed in their purpose in presenting the subject in "an elementary, clear, concise, albiet dogmatic fashion". It is a faithful presentation of the Wilson concept.

The subject of cardiac arrhythmias is omitted although, in the reviewer's opinion, the interpretation of arrhythmias is becoming a lost art both for the student and for the physician. L. S.

NEW BOOKS

Radiochemical Studies: The Fission Products, Books 1, 2, and 3. Edited by CHARLES D. CORYELL, Dept. of Chem. and Lab. for Nuclear Sci. and Engineer., Mass. Inst. of Tech., and NATHAN SUGARMAN, Inst. for Nucl. Studies and Dept. of Chem., Univ. of Chicago. Natl. Nuclear Energy Series, Manhattan Project Tech. Sect. With foreword by Gordon Dean, Chairman, U. S. Atomic Energy Comm. Total pp., 2086; many ills. New York: McGraw-Hill Book Co., Inc., 1951. Price, $18.50.

THIS 3-volume set includes information of unquestionable value to the research worker in nuclear fission. Book 1 covers Counting Techniques, Chemical Studies at Tracer Levels, Remote-Control Techniques, and Studies of the Fission Process. Book 2 is concerned with Radioactivity of the Fission Products. In Book 3 the subject discussed in Book 2 is continued. Additional topics included in this volume are Radiochemistry of the Fission-product Elements, Special Studies of Gaseous Fission Products, and Radiochemical Studies of Other Activities.

The 4 appendixes in Book 3 consist almost entirely, except for the author index, of tabular matter on A) Fission-product Decay Chains, B) Fission Yields, and C) Nuclides Formed in Thermal Fission. These tables have undoubtedly made it possible to compress into 12 pages the subject index for the 3 books.

The numbering of the illustrations to conform to a code used in a filing system (Fig. 322.7 and Fig. 322.8, or Fig. 336.15, Fig. 366.3 and Fig. 336.4, for example) is a new departure which has the advantage of employing digits in such a way that there appear to be fewer than 350 illustrations, and also of obviating the necessity of renumbering figures originally assigned to the source material. The additional burden placed on the reader, however, in following these subdivisions of figures is questionable.

Modern Dietetics. By DORIS JOHNSON, Fellow in Home Econ. Univ. of Wis. Edited by HAZEL E. MUNSELL, Ph.D., Research Worker, Bureau of Home Econ., U. S. Dept. of Agric. Pp. 529; 9 ills. New York: G. P. Putnam's Sons, 1951. Price, $4.95.

A BACKGROUND of teaching student nurses makes the author very eligible to write a textbook of dietetics for them. She should also be commended for using the new figures which have been approved by the American Dietetic Association and the American Diabetic Association for the calculation of the diet prescription for the diabetic. It would have been well if she had carried out the same procedure in the calculation of the low calorie diets. Part II, Diet Therapy, is well handled, the therapeutic diet being used as a modification of the normal diet. The references and bibliographies at the end of every chapter have been well selected. Hospital interns should find the book a practical aid. M. B.

Hope and Help for the Alcoholic. By HAROLD W. LOVELL, M.D., Assoc. in Neurol., New York Med. Coll. Pp. 215. Garden City, New York: Doubleday and Co., Inc., 1951. Price, $2.75.

THIS book is written for the lay person, the object being to present an over-all picture of the alcoholic problem. The more positive aspects of the book deal with the physical basis of alcoholism and the work done by Alcoholics Anonymous. The author's approach to the emotional problems of alcoholism is very inadequate. The title is more optimistic than the contents and it is difficult to see where the book would be an inspiration to the problem drinker. A. H.

NEW EDITIONS

Bamford's Poisons. Their Isolation and Identification. Revised by C. P. STEWART, University of Edinburgh. 3rd ed. Pp. 316; 23 ills. Philadelphia, Blakiston Co., 1951. Price, $5.50.

SOME rearrangement in the order of the chapters, additional analytical methods, and new sections on antihistaminic drugs and synthetic morphine substitutes increase the value of this practical manual of laboratory toxicologic analysis. S. E.

Textbook of Pathology. By ROBERT A. MOORE, Washington Univ. Sch. of Med., St. Louis. 2nd ed. Pp. 1048; 501 ills. Philadelphia: W. B. Saunders Co., 1951. Price, $12.50.

THE first edition (1944) has been revised with shortening (by nearly 300 pages), some rearrangement, some additional material and a few changes to bring the text up-to-date. As is usually the case the first revision is a very definite improvement. The book is now a thorough and thoroughly modern textbook of pathology, with all the good features of the first edition and fewer of the less attractive ones. It is still a very large book for students in basic pathology to master. Its arrangement, a combination of the etiologic and systemic orders,

will continue to annoy certain teachers who fail to see its logic. Those who can adapt this arrangement to their schedules will find it one of the best of the modern books in the field. E. A.

The American Illustrated Medical Dictionary. By W. A. NEMAN DORLAND, A.M., M.D., F.A.C.S., Lieut. Col., M.R.C., U.S.A., Former Member of the Comm. on Nomenclature and Classif. of Diseases of the Amer. Med. Assoc. 22nd ed. Pp. 1736; 720 ills., incl. 48 plates. Phila. and London: W. B. Saunders Co., 1951. Price, $10.00.

CELEBRATING its semicentennial, this dictionary in its 22nd edition continues to give its users the most complete coverage possible of the fast-growing medical vocabulary. Appearing in new typography and new design, there are included scores of new illustrations and thousands of new terms. Two new features which should add to the popularity of the volume are a preliminary article on Fundamentals of Medical Etymology by Professor Lloyd W. Daly of the Univ. of Penna. Classical Studies Dept., and a table of Modern Drugs and Dosage compiled by Dr. Austin Smith, Editor of the *Jour. of the Amer. Med. Assoc.* T. D.

Practical Clinical Psychiatry. By EDWARD A. STRECKER, Litt.D., LLD., M.D., Prof. of Psychiatry, Univ. of Penna.; FRANKLIN G. EBAUGH, M.D., Prof. of Psychiatry, Univ. of Col.; and J. R. EWALT, M.D., Univ. of Texas, Galveston; with Section on Psychopathic Problems of Childhood by LEO KANNER, M.D. 7th ed. Pp. 506; 35 ills. Phila. and New York: Blakiston Co., 1951. Price, $7.00.

THE authors of this textbook of psychiatry have tried successfully to make each edition better than its predecessor. The present edition presents a broad approach to modern dynamic psychiatry. Psychoanalytic contributions are more prominent than in previous editions and there is an extensive bibliography at the end of each chapter. However, there are several chapters devoted to various psychoses but only one to the psychoneuroses. Some of the others deal with the Constitutional Psychopathic Inferior, Alcoholism, and "Support" Psychotherapy. The last chapter on psychopathological problems in children is written by Dr. Leo Kanner. The authors have made a sincere effort to include at least some material from various schools of thought and have incorporated much recent research in their book. S. F.

Handbook of Nutrition. By COUNCIL ON FOODS AND NUTRITION, AMER. MED. ASSN. 2nd ed. Pp. 717; 35 ills. and charts. Phila. and New York: Blakiston Co., 1951. Price, $4.50.

THIS series of special articles on Nutrition was prepared under the editorship of Drs. Elvehjem, Youmans, and Fishbein by leading authorities in the field of nutrition for the *Jour. of the Amer. Med. Assn.* It has been completely revised since its first appearance in 1943.

All aspects of nutrition are considered, with the emphasis on the clinical application. It is divided into 4 basic parts. Part I is a consideration of the "Individual Nutrients", that is, proteins, fats, carbohydrates, minerals. Part II is a consideration of "Nutritional Needs", that is, dietary allowances and energy and nutritional requirements in infants, pregnancy, aging, and disease. Part III discusses "Nutritional Deficiencies", and Part IV covers "Foods and Their Nutritional Qualities."

Since many of the chapters have appeared in the *Journal*, most physicians are familiar at least in part with the text. The small number of illustrations is unfortunate, particularly in that section of the book dealing with diagnosis of deficiency disease in which oral, skin, and Roentgen manifestations play such an important part in the recognition of the various syndromes. However, this is a relatively minor criticism, and the book accomplishes its purpose admirably of acting as a complete handbook on this important phase of medicine. It may be recommended wholeheartedly to physicians and students. G. W.

A Text Book of Medicine. Edited by RUSSELL L. CECIL, M.D., Sc.D., Prof. of Clin. Med. Emeritus, Cornell Univ., New York, and ROBERT F. LOEB, M.D., Bard Prof. of Med., Columbia Univ., New York, together with Assoc. Editors A. B. Gutman, Prof. of Med., Columbia Univ., WALSH MCDERMOTT, M.D., Assoc. Prof. of Med., Cornell Univ., New York, and H. G. WOLFF, M.D., Assoc. Prof. of Med. (Neurology), Cornell Univ., and 163 contributors. 8th ed. Pp. 1627; 204 ills. Phila. and London; W. B. Saunders, 1951. Price, $12.00.

THIS edition includes articles on 20 subjects not covered in previous editions and 82 new treatises on subjects previously covered. There has been a regrouping of several diseases as their etiology has become clarified since the last edition. In spite of these considerable additions the total length of the book has been shortened by 136 pages without sacrificing any important material. The aim of the editors has been to encompass in a single volume an accurate discussion of those diseases comprising internal medicine. The physiological, biochemical, and psychological aspects of the diseases have been emphasized without neglecting the brief definition, pertinent historical facts, and pathological features of the diseases described. Treatment is outlined from a conservative and general point of view which is adequate for the scope of the book. This can be whole heartedly recommended for medical students, for general practitioners, and as a reference book for internists. J. L.

Functional Neuro-Anatomy. By A. R. BUCHANAN, M.D., Prof. of Anat., Univ. of Colorado Sch. Med., Denver, Col. 2nd ed. Pp. 323; 273 ills., 19 in color; Phila.: Lea & Febiger, 1951. Price, $7.50.

THE author writes in a simple style and a clear concise manner so that this book is of particular value to the medical student. The basic physiological data are present for each important central nervous system structure. Complex theories are avoided. An excellent atlas is present, which aids the student in an understanding of the study of morphology of the central nervous system. The chapter on basal ganglia is excellently written and is easily understandable. H. W.